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Original Articles

STUDIES IN HAY FEVER: SPECIFIC DESENSITIZATION OF SKIN SITES IN ACTIVELY SENSITIVE PERSONS*

HAROLD C. WAGNER, M.D., AND FRANCIS M. RACKEMANN, M.D.
BOSTON, MASS.

INTRODUCTION

IN A RECENT paper we[1] could show that the desensitization of passively sensitized sites produced in the skin of non-sensitive persons by the injection of serum from pollen sensitive patients was easily accomplished, and that in many cases this desensitization with the extract of one pollen resulted in desensitization against other and related pollens at the same time. More pertinent to the study of hay fever is the present problem which deals with the active treatment of the patients themselves rather than of the recipients of their serum. Our object was to find out whether a series of doses of pollen extract injected each day into exactly the same area of skin would result in a local desensitization, and if so, what the limitations and variations, especially in the time relationships, might be, and further, whether the extracts of different pollens would give different results in different groups of patients. Perhaps crossed reactions between different pollens could be observed as well by this "active" method as by the former "passive" method.

In 1921 MacKenzie and Baldwin[2] injected small doses of egg white and of other proteins intracutaneously into five patients sensitive to these proteins. They gave their doses at intervals of one to two hours and observed that the local reactions which followed the first few doses disappeared after five or six treatments. The previous sensitiveness had been abolished and remained so for as long as five days. In another experiment, histamine was used, and the skin reactivity persisted. The authors claimed that the exhaustion observed in the first experiment was specific.

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Cooke,[3] however, found that the reactions to repeated doses of histamine did become smaller and so questioned whether the change observed was truly specific.

In 1932, Benjamins and his coworkers[4] in Holland in a study of the hay fever producing grasses, found that an area of skin that was desensitized to one grass would then react to another grass.

Our experiments were with doses at daily—not hourly—intervals, and they were planned so for two reasons: first, because we wanted to compare them with our previous experiments with passively sensitized sites; and, second, because daily intervals corresponded more closely to the methods of treating our hay fever patients in the clinic.

METHODS

Patients were selected at random from those under treatment in the Allergy Clinic at the Massachusetts General Hospital. Most of them gave a history of hay fever from early June to the middle of July and showed good positive skin tests to all the common New England grass pollen extracts. At the same time a few patients sensitive to ragweed were studied. As said above, the method was to give a series of daily injections of the particular pollen to be studied with great care to place the injection in exactly the same skin site at each treatment. The responses observed in twenty minutes were recorded in a series of drawings, checked by measurements in millimeters of the wheals and areolae. In each case, four different sites were studied at the same time, the object being to control any minor differences in technic which might occur; and we were pleased to find that, in a large majority of the cases, the results obtained in each of the four different sites were entirely comparable, one with the other.

Groups of seven patients each were treated daily with timothy, red top, orchard grass, and ragweed respectively. The typical results are shown in the two accompanying figures.

Fig. 1 represents a summary of the observations in the seven patients treated with ragweed. The illustrations of the successive local responses represent in each case an average of the four different test sites which, as just said, gave comparable and equal reactions. A study of the reactions shows the following:

Case 1 (A. J.) responded well in that the treated spots became desensitized on the eighth day. On the seventeenth day, however, local sensitiveness had been reestablished, and eight days later it was still manifest and no doubt remained so indefinitely.

Case 2 (L. B.) showed reactions diminishing in size so that on the fifth day they were almost negative. On the eighth day, however, a dose of the same 1:1,000 ragweed gave a reaction which was even larger than

the response to the original dose. After this, daily treatment diminished the size of the response but only to a slight extent, and on the eighteenth day the reaction was again clearly positive.

Case 3 (E. A. M.) was locally desensitized to the 1:5,000 dilution on the ninth and tenth days. On the eleventh day treatment was stepped up to the 1:1,000 dilution, and for the next week doses of this were given about every other day. There was some lessening of the response, but it never did disappear during the period of observation.

Case 4 (L. L.) is like Case 2, the later doses caused not a diminution but an increase in the size of the reaction.

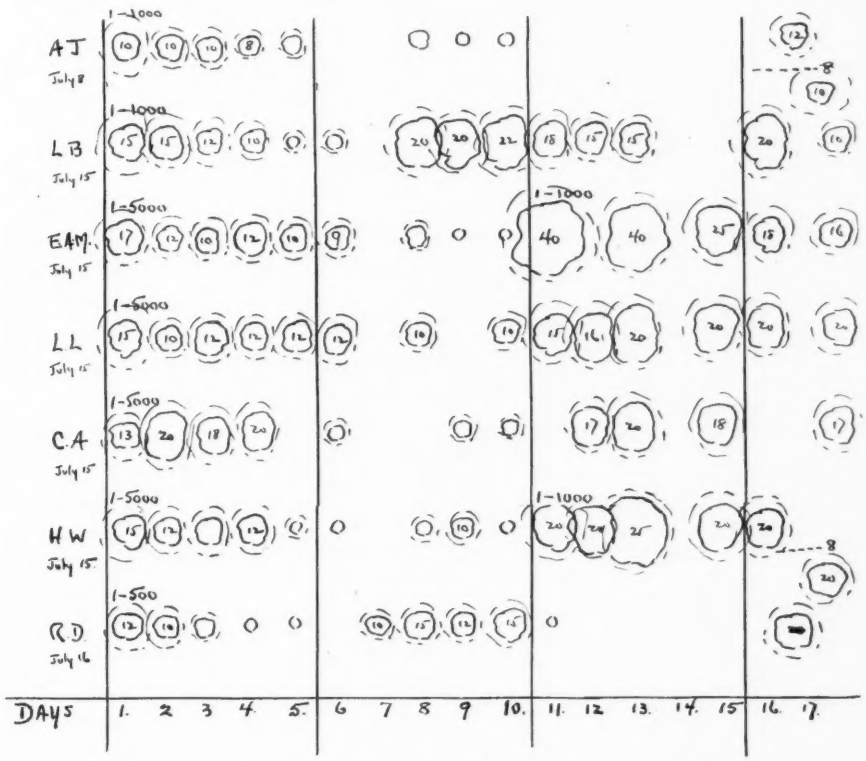

Fig. 1.—Drawings of the reactions which follow the daily injections of ragweed extract. Small numerals show the average diameter of the wheals in millimeters. The areolae are indicated roughly. The dilutions employed are indicated at the top of each line of drawings and the same dilution is used in the line until a different dilution is indicated. The dotted lines on the right ending in a figure indicate the number of days between the last regular drawing and the drawing under the figure.

Case 5 (C. A.) likewise shows a definite degree of desensitization after the first few doses, and then an increase in the reaction after the tenth day—the increase continuing to the end of the study.

Case 6 (H. W.) demonstrated a good desensitization after five and six doses of the 1:5,000 dilution with a slight transient recurrence on the eighth and ninth days. Obviously, however, the change was in degree only because when on the eleventh day the dilution was made stronger,

the reaction became larger than ever, and so remained to the twenty-fourth day, which was eight days after the last serial dose.

In Case 7 (R. D.) the reappearance and the increase of sensitiveness between the seventh and the tenth days are well shown. On the eleventh day, however, the reaction disappeared again. On the seventeenth day it was quite as large as ever.

As a whole, Fig. 1 shows that it is possible to desensitize local skin sites in patients with ragweed hay fever by repeated doses of ragweed but that the desensitized state is a change in degree rather than in kind

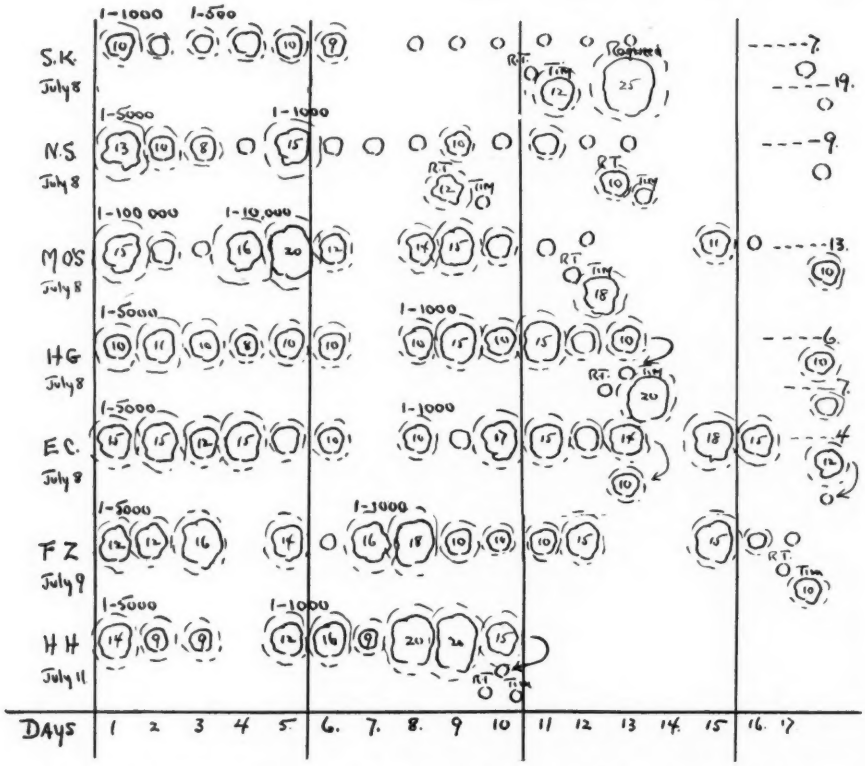

Fig. 2.—The general plan is similar to that of Fig. 1. In Cases 4, 5, and 7, curved arrows point to the reaction produced by extra doses of the same extract given in from one to two hours after the regular daily dose. "Crossed" reactions are indicated by the symbols R.T. for red top, and Tim. for timothy, placed over the extra reactions just below the regular lines.

and that its duration is always short. Further, that when sensitiveness reappears, it is likely to be more marked than before.

The increase in the size of response which occurs in several of the cases between the fifth and tenth days and even without any change in the size of doses will be discussed later.

Fig. 2 shows the reactions obtained with a series of doses of orchard grass in seven patients sensitive to the common grass pollens. Here again the drawings represent the average of the four sites treated almost alike in each patient.

Case 1 (S. K.) was treated for two days with the 1:1,000 dilution and after that with the 1:500 dilution. Desensitization was manifest on the eighth day, and this desensitization persisted through the thirteenth day. It was evident seven days later on the twentieth day and also on the thirty-ninth day. The crossed reactions shown on the chart will be described later.

Case 2 (N. S.) was easily desensitized on the fourth day to the 1:5,000 dilution. He reacted well to the 1:1,000 dilution on the fifth day and then became desensitized even to this stronger dilution and remained so throughout the experiment, up to twenty-two days except for slight breaks on the ninth and eleventh days.

Case 3 (M. O'S.) was more sensitive than the others. She, however, became desensitized first to the 1:100,000 dilution and then to the 1:10,000 dilution. On the thirteenth and fourteenth days, treatment was omitted, and on the fifteenth, sensitiveness had returned, but on the next day the reaction was negative again. Thirteen days later, she was as sensitive as ever.

Case 4 (H. G.) was never desensitized with the 1:5,000 dilution nor with the 1:1,000 dilution except that on the thirteenth day he was treated twice, that is, a second dose was given two hours after the first. This second dose failed to cause a response. The skin site was desensitized. Six days later, however, when the areas were tested again, the reaction had returned.

Case 5 (E. C.) gave no evidence of desensitization with the 1:5,000 dilution. On the eighth day a treatment with the 1:1,000 dilution produced a moderate response, and on the next day the dose revealed an almost negative reaction. After that, however, the size of the wheal was larger instead of smaller. On the thirteenth day when a second dose was given two and one-half hours after the regular daily treatment, the reaction was smaller, but it was not negative. On the twentieth day, however, a repetition of this two-hour treatment did cause a negative reaction. Unfortunately, the patient was not tested again, but one can guess that the positive phase recurred shortly after this.

Case 6 (F. Z.) became desensitized to the 1:5,000 dilution on the sixth day, then reacted well to the 1:1,000 dilution and continued to do so until the sixteenth and seventeenth days when the reactions became smaller and disappeared.

Case 7 (H. H.) was followed for only a short time. Like many others, however, the reactions were found to grow larger after the first few days of the experiment. On the tenth day a second dose given two hours later demonstrated a desensitization.

The charts of the timothy and red top groups are not reproduced herewith because the findings in each are analogous to the findings in the orchard grass group. With red top, desensitization of temporary character was established first to the 1:5,000 and later to the 1:1,000 dilution

in four cases (Nos. 1, 2, 3, and 6). In Case 4 the reactions did not disappear until on the seventeenth day when a second dose was given shortly after the first. In Case 5 the sensitiveness was slight, and treatment was begun with the 1:100 dilution. Desensitization was accomplished promptly on the fifth day. Further treatment on the eighth and ninth days gave no response, but fourteen days later on the twenty-third day, the reaction was positive again. Case 7, on the other hand, was more sensitive and was treated with nothing stronger than the 1:10,000 dilution. Partial desensitization was observed on the twelfth day, but desensitization was not complete until on the thirteenth day, a second dose was given after the first as described above. Then for the first time did the reaction become negative. Curiously, however, this patient was still negative to the 1:10,000 dilution when tested five days later, on the eighteenth day.

There were only 6 timothy cases. Four of them were desensitized quite easily to the 1:5,000 dilution, but in each case further treatment with the 1:1,000 extract caused prompt responses which persisted indefinitely and were still present seven days after the last of 15 consecutive doses. The other two cases failed to show desensitization; the local reactions continued and even became larger on the twelfth day and, two hours after the first dose, did show an absence of reaction. Desensitization could be demonstrated although later on, in nine days and seven days respectively, the reaction was positive again.

DISCUSSION

Certain general conclusions can be drawn from these findings. Desensitization of skin sites in patients actively sensitive to pollen is possible in almost every case. But the details of time, of the number of doses, and of dilution strength which are necessary to produce desensitization, vary widely among the different patients. In many instances treatment with dilute 1:5,000 material resulted in a prompt disappearance of the skin test which immediately reappeared when the 1:1,000 dilution was used, and then a longer time was required to abolish the reaction to the stronger dilution. In one or two cases the original level of sensitiveness seemed to be higher so that the 1:1,000 dilution could be used at the beginning of the experiment. To this, prompt desensitization occurred, only to find later on that the 1:100 dilution would still react. It is obvious that desensitization of this sort is a quantitative affair and not an absolute change in the reaction of the individual.

Desensitization is relative. It is also temporary. If two to three days were allowed to lapse without further treatment, new reactions occurred promptly when the same site was injected again with the same dilution but after the interval. In several cases the daily doses never resulted in a definite desensitization. In them the method of rapid desensitization was used with treatments given at intervals of one to two hours. Under

these conditions desensitization was accomplished more rapidly. One man (E. H.), for example, was given doses of the 1:5,000 timothy on each of ten successive days with no evidence whatever of any diminution in the size of the local responses. When, however, on the eleventh day he was treated at hourly intervals, desensitization was rapidly accomplished after the third hourly treatment. Similar observations were made in a total of eight other cases, and they fall in with the experiments of MacKenzie already referred to and of Alexander[5] on the rapid desensitization of horse sensitive patients and give strong support to the findings of Vaughan[6] that treatment of hay fever in the acute stage by frequent doses at short intervals works well.

Crossed reactions are another feature of this work. Fig. 2 shows that a number of patients desensitized with orchard grass were subsequently tested in the same spots with red top and timothy. In most of the cases these other tests were also negative, but it is most interesting to find that the skin sites desensitized to orchard grass would react to red top in at least one out of 6 cases, and to timothy in 4 out of 6 cases, and not in the other two. The red top chart shows similarly that sites desensitized to red top still reacted to orchard grass in each of 3 cases and that they reacted to timothy in all but one of the 7 cases. In the timothy study, desensitized sites reacted to red top in 3 out of the 6 cases but to orchard grass in only one out of 5 cases. These findings are collected in Table I.

TABLE I

CROSSED REACTIONS WITH DIFFERENT GRASS POLLENS

SITES DESENSITIZED TO	RETESTED WITH: TIMOTHY	ORCHARD GRASS	REACTED TO: RED TOP
Timothy	–	5/1	6/3
Orchard grass	6/4	–	6/1
Red top	7/6	3/3	–

In each section the first figure indicates the number of patients tested; the second figure the number of positive reactions. Thus, of 5 patients desensitized to timothy and tested with orchard grass, 1 reacted positively.

The figures as presented are unimportant. The point they bring out is that the results were not constant in the group as a whole. The variation in the recipient, in the response of desensitized sites to other related pollen extracts, was described in the former study of passively sensitized sites. The phenomenon now observed in the desensitized sites of actively sensitive patients is similar. It depends no doubt also upon the nature of the sensitiveness in that individual, and is perhaps referable to a multiplicity of antigens in the pollen itself.

Whether the results as summarized in Table I can throw light upon the question of the proper selection of pollen for treatment is doubtful. Desensitization of skin sites with either timothy or orchard grass results usually in a desensitization to the other two grasses, but the exceptions are numerous. Red top, on the other hand, is evidently not so reliable

in its ability to take care of the other grasses. Perhaps it contains a smaller proportion of the common factor. The figures as presented are, however, too small to justify much discussion.

Two special cases not included in the charts are of interest. In the case of J. F., two series of desensitizations were carried out at the same time—timothy on one arm and ragweed on the other. The timothy sites became desensitized on the fourth day and the ragweed on the fifth day, but after desensitization, the timothy site reacted to ragweed just as the ragweed site reacted to timothy. Quite analogous was another patient (A. L.) who was desensitized with orchard grass in one arm and timothy in the other. The orchard grass reaction subsided rapidly on the second day, but the timothy reaction did not disappear until the third day. When the sites were then tested with other pollens, the timothy sites retained their sensitiveness to orchard grass but did not react to red top, whereas the orchard grass sites were found to be desensitized to both timothy and red top.

The very transient character of the desensitization in these experiments deserves emphasis in connection with the treatment of hay fever. It is our experience that patients do better when the treatment is continued into the hay fever season. Evidently the effect of treatment does not last long. Furthermore, we agree with Vaughan that many patients can be relieved by one or two doses of pollen extract given after the hay fever has begun. It may be that successful results depend upon the time relations between the dates of individual doses and the dates of high pollen concentration in the air. Incidentally, we recognize that the results of pollen therapy are in no way proportional to the total number of doses or to the size of the last dose. We[7] find that the treatment must be optimal for the particular patient. It is possible that the really effective part of the pollen treatment is the last part, that is, the one or two doses which by chance are given in the right relation to the pollen incidence. These studies on the active desensitization of local skin sites would seem to strengthen such a hypothesis.

SUMMARY

1. When local skin sites in patients with hay fever are injected repeatedly with pollen extract, desensitization usually results.

2. This desensitization is always relative—never absolute. A stronger dilution will cause a reaction in sites which do not react to a weaker dilution.

3. Desensitization is temporary. The skin reaction returns in many cases if the area is left untreated for a few days.

4. Rapid desensitization may be produced by doses given at hourly intervals in those cases in which the doses at daily intervals do not cause a lessening of the response.

5. Crossed reactions between the three grass pollens common to New England occur in many cases—not in all. Their incidence probably depends upon a mechanism which is similar to that causing the variation in the recipient of passively transferred local sensitiveness.

6. The bearing of these observations on the treatment of hay fever is discussed briefly.

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DISCUSSION

DR. A. H. FINEMAN.—Have you tested these sites during the pollen season and outside of season?

DR. PHILIP LEVINE.—It may be of interest to make similar experiments except that the neutralization of reagin be carried out in the test tube.

DR. A. H. W. CAULFEILD.—If I am correct, I gathered that with the same serum you might obtain different results with different recipients.

I should like to ask whether you use any particular technic whereby you select your recipients? We take two or three serums from allergic patients whose reagin titer gave varying reactions in previous recipients. If these previous results are duplicated in a new recipient, then further tests with this last recipient will, we believe, be found comparable with those obtained with like recipients. The initial tests must of course include a normal serum and the antigen in question.

DR. F. RACKEMANN.—Dr. Fineman raised an interesting point. I thought perhaps some of our trouble was due to the fact that the actively sensitive grass cases were observed during the grass season, and there might be an absorption through the nose. The ragweed cases, however, were treated during the grass season, and in them nasal absorption was not a factor.

Dr. Caulfeild and Dr. Levine talked about recipients. There were 68 of these recipients. They were taken from the allergy clinic, were not sensitive to pollens as shown by their control tests, but were individuals who had, or had had, allergy.

STUDY OF THE PROPHYLACTIC ACTION OF AN EXTRACT OF POISON IVY IN THE CONTROL OF RHUS DERMATITIS

LIEUT. COL. J. M. BLANK, MED. RES., AND ARTHUR F. COCA, M.D.
PEARL RIVER, N. Y.

PROOF has been lacking of a specific protection against the contact dermatitis that is due to poison ivy (*Rhus toxicodendron radicans*).

Evidence constituting such proof could reasonably be sought in two ways: first, through the direct experimental demonstration, by quantitative skin tests with an active extract of poison ivy, of an increased tolerance, or immunity; and second, through a properly controlled statistical study of the influence of specific treatment (hyposensitization) upon the incidence of the dermatitis among persons daily exposed to natural contact with the plant.

In the previous investigation of this question the first method of study was found, strangely enough, not to be available, because the result of the quantitative skin tests was the same after the desensitizing injections as before. It is the second method which has been used by the students of the question, and unfortunately the conditions necessary for its proper use have not yet been fulfilled. The statement by these writers that the injected patients were exposed to contact with poison ivy, yet did not suffer ivy dermatitis, has not been accompanied by objective evidence obtained through acceptable untreated controls, who have been similarly exposed and who actually became affected with ivy dermatitis.

A fortunate combination of circumstances enabled us during the summer of 1935 to make a suitably controlled study of the influence of injections of poison ivy extract on the incidence of ivy dermatitis in the CCC Veterans Camp MC-64, Morristown, New Jersey.

From January the entire command of Company 2217-V was engaged actively in the project of mosquito control, the work consisting chiefly of drainage of swamp areas and clearing of streams, and of a necessity the men spent their active working days in areas which abound with the poison ivy and poison sumac plants, and contacts were unavoidable.

Up to April 24, 1935, there had been 129 cases of *Dermatitis venenata*, which had been accidentally caused through contact with either the poison ivy plant (*Rhus toxicodendron radicans*) or the poison sumac plant (*Rhus toxicodendron vernix*), and these cases clinically were indistinguishable. Of this group of cases, 16 had been affected severely enough to require hospitalization or rest in quarters, causing sixty-four days' loss. There was the added depressive factor, namely "morale," of the remainder of the company to be contended with.

We were confronted by quite a problem. We therefore made surveys and reconnaissance of the shifting areas where the men worked, with a view to lessening the hazards of contact. The men were provided with gloves and were cautioned to use them, and also were taught to recognize the plants and avoid the areas whenever possible. They were cautioned to use the ordinary preventives, such as common naphtha, gasoline, or ointments. They were advised and required to report promptly to the infirmary for treatment as soon as they were affected. The command was inspected frequently to discover early cases. The usual treatments were instituted, such as applications of permanganate of potassium, ferric chloride, calamine and phenol lotions, calamine ointments, magnesium sulphate or bicarbonate wet dressings, etc. Some of the men purchased proprietary medicaments. Nevertheless, we noted an increase in our noneffectives due to this dermatitis.

At this time we began correspondence out of which the following plan of study was formulated.

The exposed men, all working under approximately the same conditions, in areas contaminated with ivy and sumac, were to be listed in three groups:

Group A was to receive four injections, at weekly intervals, of 0.5 c.c. of almond oil, containing 10 per cent by volume of acetone and 0.1 per cent of solids extracted from poison ivy leaves with acetone and freed from chlorophyl;*

Group B was to receive four weekly injections of 1.0 c.c. of a similar extract containing 0.66 per cent of the poison ivy solids (12 times the amount given to Group A);

Group C was to receive no prophylactic injections.

All these men were to be divided into gangs of 20 or more, and the groups were intermingled, so that the three groups were all part of each gang of men on the project. In such way, no group was in any area where poison ivy and poison sumac were more prevalent than in the others.

From the beginning of the experiment, as the men presented themselves with ivy dermatitis, they were to be treated in rotation: (1) with the stronger ivy extract, (2) with the weaker extract, (3) with almond oil containing only 10 per cent of acetone in the same quantity (0.5 c.c.).

The prophylactic and therapeutic injections were begun on June 17, and shortly after this there was a decline in the number of cases and in the number of days lost on account of ivy dermatitis, which continued steadily until the first of August when the incidence of this condition reached zero.

There were no cases in the month of August and only one in September, in a man who had not received any injection of ivy extract.

*All the materials used in this investigation were obtained through the courtesy of the Lederle Laboratories, Inc., Pearl River, N. Y.

Table I shows the incidence of ivy dermatitis with the number of men confined to quarters on account of it, as well as other data revealing its relative importance as a cause of disability in the camp.

TABLE I

INCIDENCE OF IVY DERMATITIS AND COLLATERAL DATA

	JAN.	FEB.	MAR.	APR.	MAY	JUNE	JULY	AUG.
Patients, all causes	221	228	297	186	329	397	427	147
Patients, dermatitis ven.	3	7	55	64	104	193	163	0
Treatments, all causes	227	242	411	330	546	690	825	418
Treatments, dermatitis ven.	9	21	171	200	325	439	321	0
Patients, in quarters, all causes	16	21	22	22	40	21	26	54
Patients, in quarters, dermatitis ven.	1	–	6	9	14	10	6	–
Days lost, all causes	51	65	80	70	132	90	51	141
Days lost, dermatitis ven.	7	22	18	30	44	28	32	0

From the data in Table II one can judge the effectiveness of the prophylactic injections during the first six weeks of the experiment.

TABLE II

THE INCIDENCE OF IVY DERMATITIS IN THE THREE GROUPS DURING THE SIX WEEKS FOLLOWING THE COMMENCEMENT OF THE EXPERIMENT

GROUP	TREATMENT	NUMBER OF MEN AFFECTED WITH DERMATITIS
A 45 men	4 × 0.5 c.c. 0.1% ivy extract	9
B 40 men	4 × 1.0 c.c. 0.66% ivy extract	3
C 45 men	None	30

It is seen that of the untreated men of Group C, 66⅔ per cent became affected with ivy dermatitis; whereas among the two treated groups of equally exposed men only 20 per cent and 7 per cent respectively were affected.

The percentage of the affected controls (66⅔) corresponds closely with the percentage of adults who have been found by skin test (patch or contact test) with strong extracts of poison ivy to be sensitive to this plant (Spain, 65 per cent; Deibert, 58.8 per cent).

It is seen also that protection was established in a greater proportion of the group that received the larger dose than it was in those receiving only one-twelfth that dose.

One may be tempted to interpret the almost complete disappearance of ivy dermatitis during the months of August and September as indicating the establishment of a complete protection in all the injected men. Unfortunately, however, there were too few uninjected controls during that period to validate such a conclusion. All but 12 of the

original 130 men had received either prophylactic or therapeutic injections of ivy extract previous to August 1. Most of these 12 men were transferred during August and early September to other localities.

CONCLUSIONS

The results of the experiments described demonstrate that injections of an extract of poison ivy (*Rhus toxicodendron radicans*) can establish a complete immunity to the usual direct contact with the plant in at least a considerable proportion of susceptible persons.

Since the men were in contact also with poison sumac (*Rhus toxicodendron vernix*), it seems probable that the immunity extended also to this variety.

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STUDIES IN CONTACT DERMATITIS*

II. Adhesive Plaster Dermatitis: Clinical and Immunologic Observations on Patients Sensitive to Adhesive Plaster

Max Grolnick, M.D.
Brooklyn, N. Y.

INTRODUCTION

In a previous communication[1] the clinical problem of irritation by adhesive plaster was discussed, and reference was made to the work of earlier investigators on the nature of the irritative phenomena caused by adhesive plaster. There was presented a technic for testing by the surface or contact method those subjects in whom adhesive plaster produced a dermatitis. In principle this procedure consisted in stamping out a ring of some liquid adhesive or fixing agent around the test substance by means of a glass tube, and then sealing the test with a disc membrane cut from some impermeable or almost impermeable material. Several combinations of coverings and fixing substances were suggested.

The need for clarification of the term dermatitis as it was applied to the manifestations of adhesive plaster irritation was stressed, and it was suggested as a result of certain impressions gathered from studies in the past five years that adhesive plaster dermatitis was of two types: (a) specific (contact dermatitis) and (b) nonspecific. In the present report there will be presented the data which formed the basis for the foregoing statement. The results of tests with adhesive plaster on normal skins will be given. In addition a special study was carried out on a group of individuals who were definitely sensitive to adhesive plaster. The nature of the etiologic factors which come into play in the causation of adhesive plaster irritation will also be presented.

PREVIOUS INVESTIGATIONS

Investigations of the nature of adhesive plaster irritation have been made in the past. While much of the literature was subject to the criticism that a confusion of terminology existed and that details of investigative procedure were not given, the pertinent references will be included in this paper for the sake of completeness of the presentation.

Siemens[2] tested two patients suffering with adhesive plaster dermatitis and found one to be sensitive to dammar resin and the other to fixed

*From the Department of Applied Immunology, Jewish Hospital of Brooklyn.
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resin acids, and ethereal oils. Later[3] he continued these studies to determine which constituent of the dammar, the resin or the acid, caused the irritation. He investigated three cases and found that the resins, and not the resin acids, produced the greatest skin reactions, though the latter at times caused mild ones; also that one subject showed stronger and another weaker reactions, and that one of the subjects presented a focal lighting up of the previous "papulous eczema" area (due to adhesive) and of the previously tested skin sites when they were retested.

Bloch, quoted by Siemens, found 11 persons sensitive to leukoplast (a foreign brand of plaster) among 1,100 patients, most of them eczematous individuals. In a group of 800 normal persons three were found who were unable to tolerate adhesive plaster. This report, however, was not clear as to whether a specific type of sensitivity was implied.

Jantzen[4] described the case of a female patient whose feet had been strapped by adhesive tape. The feet itched all night and were found to be swollen the next morning. Removal of the strapping revealed an erythematous induration, elevated about one-quarter inch, with superimposed vesicles. Sever[5] mentioned the occurrence in two blonde women of a vesicular dermatitis which followed strapping of the ankles. Swelling extended up to the knees. Brown[6] reported the case of a female patient, forty-nine years of age, in whom the application of adhesive plaster had on several occasions produced severe itching within twenty-four hours. Examination had revealed patches of closely set vesicles on an erythematous base. Control tests with other grades of adhesive plaster were negative. Montgomery and Culver[7] reported two patients with a local dermatitis at the site of adhesive plaster application, the dermatitis in one instance persisting for four weeks. A third subject reacting to adhesive was, in addition, sensitive to turpentine. The authors assumed that the resin in the adhesive plaster was the offending substance.

Unna[8] following up the work of Siemens tested 22 healthy persons with five different plasters containing dammar or other resins. He concluded from his results, without giving any details, that dammar plaster can irritate, and that the sensitivity was acquired through intermittent application of adhesive plaster. Another group of 100 persons was tested, and four showed irritation. These were women, of whom two showed a strong reaction (4° to 5° Bloch). On the whole, there was a lack of irritation by zinc guttaplaster and resin-free rubber plaster.

Vallette[9] reported a generalized exfoliative dermatitis following plaster application. Gougerot[10] cited two instances of plaster dermatitis.

Van Cleve[11] studied two patients who had developed a severe dermatitis after a forty-eight-hour application of adhesive plaster. One was tested with zinc oxide ointment, zinc oxide powder, zinc stearate, adhesive plaster, dry and moistened orris root, and a 50 per cent orris

root in petrolatum. The orris root and plaster tests were positive in twenty-four hours. The second patient was tested with zinc oxide, adhesive plaster, and orris root. The latter two tests were positive in twenty-four hours. Van Cleve likewise did patch tests with adhesive plaster and with orris root on 105 unselected patients from the dermatology ward of the Cleveland City Hospital. All subjects gave negative readings after one week. He stated that eruptions following the use of adhesive plaster were usually explained on a mechanical basis, and added that with the more general use of the patch test many cases of such eruptions would fall into the group of sensitization dermatitis.

Schwartz and Peck[12] made a study of adhesive plaster reactions using as their subjects 120 employees in a factory which manufactures adhesive tape. One-inch square patches of eight varieties of adhesive plaster were placed on the backs and arms of these subjects and were removed in forty-eight hours. The sites were inspected at this time and again forty-eight hours later. Sixty-three persons showed some reaction ranging from an erythema to an erythema with edema and vesicles. Twenty-one of these subjects were tested with 11 ingredients found in various brands of adhesive plaster, namely, South American para rubber (previously milled, washed, and dried), starch, lanolin, orris root, I-rosin, olibanum, gutta siac, beeswax, "burgundy" pitch, zinc oxide, and wood resin. The patches were left on for forty-eight hours and again inspected seventy-two hours later.

As a result of these tests one subject developed a generalized reaction, so that individual tests could not be distinguished. Of the remaining 20 subjects 7 showed no reactions. Thirteen gave positive reactions as follows: 8 to wood rosin, 8 to "burgundy" pitch, 6 to I-rosin, 5 to rubber, 2 to beeswax, 2 to olibanum, and 1 each to lanolin, orris root, and gutta siac. The authors concluded that the chief irritants were rosin and smoke-cured wild rubber. They added that skin reactions from the use of adhesive plaster were of frequent occurrence, there being two types of reactions, one due to trauma and maceration, and the other an eczematoid phenomenon due to hypersensitivity to one or more of the ingredients of adhesive plaster.

PRESENT INVESTIGATION

A number of years ago, I began a series of studies into the nature of adhesive plaster dermatitis. It was necessary to obtain for selective testing by the special technic previously described[1] a group of individuals who showed this phenomenon. Three well-known brands of adhesive plaster were used for testing at the beginning of these experiments, but when it was found that reactions to all brands were about the same, the subsequent work was carried on with only one adhesive plaster. Two hundred and seventy-five individuals were taken at random among nurses, physicians, patients in the allergy clinic, and

patients in the medical wards. Young and older adults of both sexes were utilized. When these subjects were first tested, it was not known whether any of them were disturbed clinically by the application of adhesive plaster.

Squares of adhesive tape measuring $1\frac{1}{2}'' \times 1\frac{1}{2}''$ were applied to the flexor surface of the forearm or lateral surface of the arm for twenty-four hours. The patches were removed and then observed at intervals of twenty-four hours or more, for one to several weeks. Such findings as itching, erythema, papulation, infiltration, vesiculation, pigmentation, and desquamation were observed.

An attempt was made to correlate reactions with such factors as family history of allergy, previous use of adhesive plaster, ability to tan, dermographia, color of eyes and hair, and texture of the skin. A summary of these observations and interpretations follows.

1. The average mild reaction, when it occurred, consisted of pruritis, erythema, and at times tiny papules. These were occasionally followed by pigmentation which appeared several days after the initial reactions, and were usually more marked when the original irritation was stronger.

2. The ability to react to adhesive plaster was unrelated to family history of allergy, to previous use of adhesive plaster, and to dermographia.

3. The production of pigmentation could not be correlated with the ability of the subject to tan on exposure to the sun. There was no relationship between the color of the hair or eyes, or shade of skin, and the ability of the subject to react to adhesive plaster.

4. More females were subject to irritation than were males.

5. Young adults showed irritation in greater numbers than did older adults. The thin, paperlike atrophic skin of old age rarely showed any irritation.

6. Among the 275 persons tested, one in six showed some phenomenon of irritation. This varied from a mild degree of erythema with or without papules to a more pronounced irritation with induration and tiny vesicles which were followed by desquamation and pigmentation of several days' to several weeks' duration. By far the greater number reacted only with a mild erythema.

7. It did not seem possible to group the subjects, most of whom were tested on more than one occasion at intervals of a few weeks to a few months, according to the intensity of irritation produced. Such variable factors as the location of the test site, the atmospheric temperature and humidity, and the presence of lanugo on the skin seemed to influence the degree of irritation so that subjects did not show the same amount of irritation at different testings. Usually the individual who could not tolerate adhesive plaster mentioned this fact before the patch was applied. Only a few such instances were noted.

PHARMACOLOGY OF ADHESIVE PLASTER

Adhesive plaster is described in the U. S. Pharmacopeia X as a mixture of rubber, resins, and waxes, with a filler of an absorbent powder, such as zinc oxide, orris root, or starch. The sources of these substances, together with other pertinent facts, will be briefly presented.

Rubber is a mixture of several substances occurring in the coagulated latex or milk juice of certain tropical plants (trees, vines, shrubs) growing chiefly in South America, Central America, Mexico, West Indies, India, Ceylon, East Indies, and Africa. The Hevia Braziliensis is one of the chief sources of para rubber. Rubber which is obtained from the Far East is plantation grown, and is also used in the preparation of adhesive plaster. Most of the standard texts devoted to the rubber industry give detailed information as to the method of collection, preparation, etc.

Rosin (U. S. P. Resina) is the residue left after distilling the volatile oil from the oleo resin obtained from various species of the pine family, mainly the southern pine. Resin is thus obtained when the oil is distilled off from turpentine.

Olibanum, a gum oleo resin, is derived from small trees of the Bosswellia species of the family *Burderacea*, growing in Somaliland and Arabia. It has in times past been referred to as frankincense. The composition of olibanum is different from that of native rosin.

Lanolin (anhydrous) is purified wool fat free from water. The wool of the sheep contains 10 per cent to 50 per cent of its weight in fat. Lanolin is a mixture of the cholesterin esters of the several fatty acids contained in ordinary fats.

Yellow wax (beeswax) is obtained by melting and purifying the honeycomb of the bee.

Balata is a raw gum material resembling gutta-percha and is used as a substitute for it. It is derived from the latex of the bullet tree, *Mimusopa Balata*, a near relative of the gutta-percha tree. It is native in the West Indies and South America and grows abundantly in Guiana.

The two remaining constituents in adhesive plaster are zinc oxide and starch. Orris root, commonly used in the past as a filler, was not used in this series of tests. The term pitch denotes a compounding of rosin, beeswax, and lanolin.

For purpose of testing, the following substances were prepared in the percentage strength which each occupied in adhesive plaster mass. It was deemed advisable to use these concentrations in order more nearly to parallel the simple adhesive plaster test. Balata, lanolin, olibanum, pitch, rosin, and rubber were put up in a petrolatum base. A mixture of rosin, olibanum, and pitch (mixed resins) in petrolatum was also used. Yellow beeswax was dissolved in ether. Zinc oxide and starch in

powder form were merely moistened before test application. Specimens of adhesive plaster mass were also used. All materials were supplied by one of the leading adhesive plaster manufacturers.

Of the group of 275 subjects tested, the 24 showing the strongest reactions were selected for testing by the special technic with the adhesive ingredients mentioned above. The tests were made on the lateral surface of the arm and left in situ for twenty-four hours. The sites were then examined, and reinspected at intervals of one or two days for a minimum of two weeks.

Only two subjects were found to react positively to one or more of the test substances. Both individuals, prior to any testing, volunteered the information that they were sensitive to adhesive plaster. In addition, five known adhesive sensitive individuals who eventually showed positive reactions to the adhesive constituents were added to the present study. They were not selected from the group of 275 persons routinely tested with adhesive plaster.

CASE STUDIES

The case histories and the results of testing the seven subjects who were studied follow.

CASE 1.—N. H., female, aged thirty years, office assistant, had had her ankle strapped for a sprain about eight years ago. She was unable to keep on the strapping longer than twenty-four hours. An intense dermatitis was present which persisted for many weeks. Previous to the above episode, adhesive had been used for minor things only, as for a cut, but never for any extensive strapping. For the past few years she had been handling adhesive plaster, as assistant in the office of an orthopedic surgeon, but had encountered no ill effect. She was extremely careful after handling adhesive plaster to wash her hands thoroughly with soap and water. The patient had been subject to severe poison ivy dermatitis as far back as she could remember.

The test substances were applied on March 11, 1932, using the cellophane-collodion technic.[1] Rosin, olibanum, and pitch were used in only 10 per cent strength, since it was known from the experience of earlier investigators that resins were the irritant substances in plaster. All sites were negative in 24 hours. Rosin became positive at 36 to 48 hours, pitch at 48 to 60 hours, and olibanum at 60 to 72 hours. The maximum intensity (3°) was reached at 96 hours. After six weeks, pigmentation was still apparent over each of the positive sites.

In doing some further tests with a fresh supply of cellophane discs, many positive reactions were noted. These reactions were finally traced to the cellophane itself. This was of the moisture-proof variety, which has a surface coating containing a resin. Repeated check tests, using only the cellophane patch, proved this finding. The sites were negative at 24 hours, positive (2°) at 48 hours, and at maximum intensity (3°) in 72 hours. Pigmentation was present more than one week.

On Feb. 7, 1935, the subject was retested completely. The resins were used in the original strength as supplied. Three types of regular adhesive plaster were applied. Tests with 10 per cent orris root in vaseline, with moisture-proof cellophane, and with seven common contact allergens were likewise made. In 24 hours an erythema (1°) had been produced by adhesive mass, rosin, olibanum, and rubber ?,

while the adhesive plasters showed erythema and slight papulation. The remaining tests were negative. Twenty-four hours later, the plasters, rosin, olibanum, and adhesive mass showed a distinctly stronger reaction (2° to 3°), the cellophane only an erythema with scattered papules. The remaining tests were negative. All reacting sites were still positive on the fifth day after initial application. On the ninth day all previously positive sites, with the exception of cellophane, showed flaking of the skin which was brought out by stroking over these areas with a tongue depressor.

CASE 2.—A. T., female, aged nineteen years, was selected early in 1932 from a group of student nurses as one showing irritation from adhesive plaster (2° to 3°). The subject volunteered the information that she could not retain adhesive on her skin. She had first learned of this intolerance to adhesive three years before when an ankle had been strapped. The plaster had to be removed in 24 hours. A severe dermatitis was present which took several weeks to heal and left a brown pigment. At a subsequent date, adhesive kept on for a few days produced an ulcer of the skin. She apparently had not had any previous gross contact with adhesive plaster.

There was a negative personal and family history of atopy. Since the age of eight or nine, she had been subject to poison ivy dermatitis. In addition, at the age of fourteen she had a dermatitis of one forearm where she had held a bunch of flowers picked in the woods.

The patient was tested April 15, 1932, with the ingredients of adhesive plaster. The test sites were all negative for a period of at least two weeks. Several months later, rosin, olibanum, mixed resins, and rubber were applied for 48 hours. A 2° mild reaction was seen at the site of the resin only. This site later became pigmented.

On Feb. 19, 1935, tests with the following were made: rosin, mixed resins, pure rosin (small piece), moisture-proof cellophane, and plain adhesive. The test patches were removed in 24 hours, showing a 2° reaction for the pure rosin, an erythema for the cellophane, and a 1° to 2° reaction for the adhesive. Twenty-four hours later the pure rosin showed a 2° to 3° reaction, and the cellophane only an erythema. At the end of one week there was still evidence of reaction at the site of the pure rosin, but not at any of the other sites.

The patient was seen by me on Oct. 1, 1935. She mentioned that she had had an appendectomy six months previously. Three strips of adhesive plaster had been kept on the abdomen for a week, with the production of only a slight itching. On removal the skin appeared red, though there was no irritation comparable to what had occurred in the past.

CASE 3.—H. G., male, aged thirty years, a physician, was selected from the group of 275 persons tested with adhesive plaster. He mentioned at the time of testing that he knew his skin would be irritated by adhesive plaster. Several years before, following an appendectomy, the adhesive plaster dressing had to be removed 24 hours postoperatively because of intolerable itching. The patient was a hay fever sufferer.

In June, 1933, he was tested with the ingredients of adhesive plaster, and with moisture-proof cellophane. The patches were removed by the subject and were not seen by me until 96 hours after application. A few tiny papules and slight pigmentation were seen at this time over the sites of rosin and pitch. These reactions were considered as questionably positive. Since the 24 hour application of adhesive plaster at the end of two and one-half weeks had shown pigmentation and definite scaling, it was felt that this was a case of a true sensitive dermatitis. Tests with the following substances were again done: adhesive mass (fresh), mixed resin, pure rosin, wax, rubber in vaseline. In 24 hours fresh mass and pure rosin pro-

duced an erythema. In 72 hours mass and mixed resins showed a 2° reaction and the pure rosin a slightly stronger reaction. All sites finally went on to desquamation and could be readily detected by rubbing the surface with the finger nail or a wood stick, thereby causing slight flaking of the skin.

Retesting on April 19, 1934, revealed the following findings: in 24 hours, rosin and olibanum negative, mixed resins 2°, rubber ?, pure rosin 1° to 2°. At the end of one week there was still evidence of positive reactions. It was also noticed that the subject had shown some irritation to the liquid adhesives used in patch testing, reacting very mildly to collodion, and mildly though more definitely to frisket and duo adhesive. This irritation was in evidence only at the margin of the disc and did not spread. Never did it interfere with the proper interpretation of the tests. To determine whether this subject was specifically sensitive to these liquid adhesives, individual tests with collodion, frisket, and duo were repeated several times, but no reactions were obtained. Blank test patches did not produce any reactions. It must be concluded that a nonspecific factor could play some part in a dermatitis of the specific type.

On Jan. 10, 1935, the patient informed me that for a few weeks he had noticed a dermatitis of the proximal phalanx of the finger on which he had been wearing a white gold ring for a few months. There was a well-localized dermatitis of the contact type at the site mentioned. Tests with a number of contact excitants revealed a 2° to 3° reaction to nickel. The latter is one of the metals in the alloy, white gold. Rubber and pure rosin were again tested. The former was negative and the latter gave a 3° reaction. A test with 50 per cent orris root in vaseline was negative.

CASE 4.—J. M., male, aged twenty-three years, a college student, was seen by me on Nov. 14, 1933, for a vesicular dermatitis involving the intergluteal fold, extending to the perineum and scrotum. For ten days he had been using a rectal ointment (Dorb's pile ointment) for hemorrhoids, with considerable relief for the first week. The skin then began to itch, ooze, and there was considerable local pain. There was a negative personal and family history of atopy. A contact test with the ointment yielded a 3° reaction. The adhesive covering showed a 2° to 3° reaction. The patient stated that he had previously used adhesive plaster with impunity.

Tests with the ingredients of this ointment were then made, namely with sulphur, zinc oxide, resorcin, galls, stramonium, krameria, and oil of cade. Positive reactions were obtained with oil of cade and krameria. A number of common contact excitants were likewise applied, but only poison ivy gave a positive reaction. When the patient was informed that he was sensitive to several external medicinal agents, he recalled that on two occasions in 1930, ointments prescribed by a physician for an axillary ringworm had to be discontinued because they had produced local swelling and blistering.

On Feb. 13, 1934, testing with the adhesive plaster components gave a 2° to 3° reaction (at the 96th hour) to rubber only. On March 23, 1934, tests were repeated, and the following results were obtained: no reactions in 24 hours; the 48 hour reading showed an erythema (1°) for rosin, mixed resins, rubber, and pure rosin. In 72 hours rosin (in vaseline) and pure rosin showed a 1° to 2° reaction and rubber a 3° reaction. At the 96th hour the reactions to rosin were stronger (2° to 3°), that to rubber persisting. On the ninth day only the site of the rubber test could be seen. However, by rubbing with the finger nail over the general area that was tested, flaking of the skin at the previously positive sites could be brought out. It was interesting to note that frisket and duo, both rubber containing adhesives, did not produce more than a transient erythema when they were used in patch testing this patient.

The subject was again seen on Sept. 30, 1935. Adhesive plaster gave a mild reaction (1° to 2°) which was nearly gone in 96 hours. Rubber, rosin, and pitch at the 24th hour reading showed an erythema. This was faded at the 96th hour.

The patient again appeared at my office Nov. 20, 1935, with a vesicular dermatitis in both axillae. He had been using a deodorant, yodora, for three days, beginning one week previously. On the fifth day the rash began to appear. The patient did not return for further study.

CASE 5.—H. B., female, eighteen years of age, a technician in a pathological laboratory, was seen on March 8, 1934, for a dermatitis of both hands of nearly one year's duration. There was a negative personal and family history of atopy. She had been working in the tissues department of the laboratory for several weeks when the rash appeared and then spread to the dorsum of both hands and between the fingers. Eight contact substances were tested, among them formalin. This was the only positively reacting substance. It was noted that the adhesive plaster gave a 3° reaction, causing a little difficulty in reading the tests. In attempting to continue the testing with other substances, using substitute technics, duo was found to cause a distinct reaction and had to be discarded. It was subsequently learned that a small amount of formalin was at times employed as a preservative for the duo adhesive. There was no reaction to either collodion or frisket cement.

Testing with the ingredients of adhesive plaster revealed negative findings in 24 hours. A 72 hour reading showed a 2° reaction to rosin and mixed resins, but none to rubber. Cellophane was negative. The patient was considered as a case of formalin dermatitis with adhesive plaster (rosin) sensitivity.

CASE 6.—J. M., female, aged thirty-four years, a laundress, was strapped for a chest ailment. In three or four hours the itching and pain were so severe that the patient herself had to remove the adhesive strapping. When seen by me two days afterward (Dec. 31, 1934), there was a marked vesicular dermatitis over the site of plaster application. Desquamation continued for at least three weeks.

There was a negative personal and family history of atopy. The patient, on being questioned as to previous experiences with adhesive plaster, admitted knowing she was sensitive to adhesive plaster, but had failed to mention this when her chest was strapped. Six and one-half years before, a breast abscess was opened and the dressing kept in place with adhesive tape. The latter had to be removed the next day because of pain and itching. An extensive blistering took more than two weeks to heal. Since this episode she had never been able to use adhesive plaster. Eleven years before, she had had a laparotomy, but adhesive plaster had caused no trouble at that time.

The patient stated that perfumed soaps would produce a pimply rash on the skin, though she could tolerate the ordinary white soaps which were unscented. About ten years ago she had developed a rash on both thighs which she thought was a laundry irritation. A change of laundries was accompanied by a prompt clearing up of the condition.

As a preliminary to testing, a small square of adhesive plaster was placed on the arm. The patient was compelled to remove it within two hours because of intense itching. When she was seen in 24 hours, a severe dermatitis was present. The ingredients in plaster were then applied for testing. Rubber had to be removed in three hours, and the others at varying intervals during the 24 hour period, because of pruritis. The first reading showed a 2° to 3° reaction for rubber, the other sites being negative. Rubber was positive for at least a week. It is of interest to note that duo and frisket adhesive showed a 1° to 2° reaction, which was strictly localized, and therefore did not interfere with the test readings.

One week later the patient was tested with moisture-proof cellophane, rosin in vaseline, and pure rosin. Removal of the patches in 24 hours revealed a slight erythema at each test site. The 48 hour reading showed a 2° reaction for both rosin tests and a 1° to 2° for the cellophane. Reactions were still evident at the end of one week.

CASE 7.—J. E., male, aged thirty-two years, a truck driver, was under the care of another physician who was kind enough to allow me to do the special tests on his patient (Jan. 14, 1936). He had had a rash on the hands for sixteen years, on both feet for seven years, and on the forehead for two months. There was a negative family history of atopy. When the regular patch tests were about to be applied to the skin, he volunteered the information that five years before he had had a severe blistering of the skin where adhesive had been used to cover a surgical dressing on his jaw. Since then, if adhesive was used, it could not be kept on for longer than 24 hours. There had been no gross contact with adhesive prior to the first episode. The patient had been variously employed as a helper in a printing place where seals were made (he worked at the blending of thick inks), as a tinsmith and roofer, and then as a driver delivering typewriter machines.

The technic with duo adhesive and rubber-faced cloth was used. Tests were performed with a large number of common contactants and with the ingredients of adhesive plaster. Positive reactions were obtained as follows: nickel 3°, rotogravure ink 3°, oil of cade 2° to 3°, moisture-proof cellophane 2° to 3°, rosin in vaseline 3°, rubber 3°, olibanum 1° to 2°. The 3° reactions exhibited marked infiltration. I was informed that desquamation persisted for several weeks.

TABLE I

RESULTS OF TESTING IN ADHESIVE SENSITIVE CASES

SUBJECT	CLINICAL DERMATITIS	ROSIN	RUBBER	MOISTURE-PROOF CELLOPHANE	OTHER POSITIVE CONTACTANTS
N. H. female	Poison ivy dermatitis	+	–	+	Poison ivy
A. T. female	Poison ivy dermatitis. Plant rash	+	–	(?) +	Poison ivy
H. G. male	Dermatitis (local) due to white gold ring and metal wrist band	+	–	–	Nickel
J. M. male	Perineal dermatitis due to a hemorrhoidal ointment. Axillary dermatitis due to deodorant	+	+	–	Oil of cade Krameria Poison ivy
H. B. female	Chemical dermatitis	+	–	–	Formalin
J. M. female	Laundry rash. Rash due to perfumed soaps.	+	+	+	Not tested
J. E. male	Dermatitis of hands, forehead, legs	+	+	+	Nickel, oil of cade, rotagravure ink

Table I represents a summary of the foregoing results obtained by testing the seven adhesive sensitive subjects. Rosin was positive in seven instances and rubber in three (Cases 4, 6, and 7). No positive reactions were obtained to any of the other ingredients of adhesive.

In order to demonstrate how tension and friction produced by the application of adhesive plaster could be factors in the production of

plaster irritation, the following experiment was done. Twelve persons were selected at random. Adhesive tape was applied as for a pleurisy or sacroiliac strapping, using considerable pull as the plaster was put on the skin. In addition, several short strips were placed on the arms of each subject, no tension being exerted. The strappings and strips were kept on for periods of five to ten days. On removal the simple arm strips showed little or no irritation, whereas the clinical strapping showed irritation ranging from redness, folliculitis and papule formation, to an actual breaking of the skin. The ends and edges of the lengths of plaster produced the greatest amount of injury, such as blebs or skin excoriation. Such signs of irritation were in evidence even on patients in whom the simple arm strips had revealed not even an erythema. Evidently pull and friction on the skin are factors which help to produce irritation of the skin.

DISCUSSION

Definition.—The term dermatitis, as it has been applied until recently to reactions of the skin resulting from the application of adhesive plaster, has been loosely employed. It would appear from the foregoing work that there are two forms: (1) a specific dermatitis of the contact variety in which the subject reacts to the gum resin or rubber constituents of the adhesive plaster; and (2) a nonspecific irritation or dermatitis in which none of the component parts of plaster produce a typical positive contact reaction. The first presents the complete picture of a dermatitis venenata with itching, redness, edema, vesiculation, desquamation, and even denudation of the skin. The latter is of short duration with itching, erythema, papulation, and rarely vesicle formation and skin denudation.

A. *Nonspecific Adhesive Dermatitis.*—The nonspecific variety may be explained as caused by the interplay of mechanical factors, such as tension, friction, maceration due to heat and moisture, retained secretions, scratching, skin infections, breaking down of skin capillaries, and others. The application of adhesive plaster to the skin brings the plaster mass into close contact with the outer skin layer (epidermis). With the softening of the mass due to body temperature and the retention of normal skin secretions under the plaster, the epidermal layers become softened. The process may lead further to inflammation and infection. When tension is applied with adhesive plaster, the skin in addition is compressed and the circulation in it is interfered with. Blood capillaries are broken down, vesicles are formed, and even denudation of the outer skin layers is produced.

B. *Specific Adhesive Dermatitis.*—The term specific adhesive dermatitis is meant to signify a hypersensitiveness of the skin to adhesive tape which has been acquired. Strauss[13] in producing artificial sensitization to poison ivy in newborn infants observed that the first application of

the patch test for a period of six to eight days did not produce any evidence of adhesive irritation in 119 infants tested. After an interval of two to four weeks 48 of these infants were retested, the poison ivy patch remaining in place for two to three days, when it was removed by the parent. The infants were seen one week after the test application. Thirty-five showed positive reactions to poison ivy, the reacting site being strictly limited to the area of the glazed paper square. Strauss[14] states that this time also there was no evidence of any irritation from the adhesive plaster covering.

It has come to my attention from the records of one of the largest adhesive plaster manufacturers that among some 200 workers engaged in manufacturing plaster, in both the making of the compound as well as the handling of the spread product, not a single case of dermatitis has been reported in many years of operation. The raw rubber is manipulated by hand in the washing, drying, and grinding processes. The mixing of the pitch also entails the use of the bare hands. I personally inspected the entire process of manufacture and was able to observe the constant contact of the workers with these raw materials.

While the incidence of adhesive dermatitis is not a high one (*infra*) it seems difficult to explain the absence of sensitization to the offending adhesive plaster ingredients among workers in the mill. Also, the seven cases reported here did not show any repeated or constant contact with the sensitizing substances. It would appear, then, that rosin and rubber, as excitants of contact dermatitis, are poor sensitizers, quite unlike the dyes, for which there is a high incidence among fur dyers, and unlike poison ivy for which a short contact is sufficient to sensitize.

This view might further be substantiated by the fact that the intensity of the reactivity to the offending substances was so variable. Cases 1 and 2 reported by Siemens,[3] and my own Cases 1, 2, 3, 4, 5 showed a fluctuation in reactivity. Since an attempt to use a standardized technic was made in the cases I tested, it would appear that some "constitutional variability" existed for each subject. I, however, am convinced that a standardization in technic for surface or patch testing in general, as it pertains to the concentrations of test substances, the amounts to be used, the method of application, etc., and a complete reporting of the details of any technic employed are essential to the proper evaluation and comparison of results.

A review of the seven case reports given above seemed to indicate that adhesive dermatitis of the specific type occurred more readily in persons manifesting some other form of contact dermatitis. It would appear that persons with adhesive sensitivity are prone to show sensitivity to other common contact substances, or vice versa.

It was also to be noted that in a few instances in the cases reported the individual tests were only faintly positive, yet the adhesive plaster

at the same application caused a marked local reaction. One must consider the possibility that nonspecific factors may play a part in cases of specific sensitivity. Furthermore, adhesive mass is not the simple addition of individual substances, but represents another compound product which may act differently from any of its constituent parts.

Incidence.—I was impressed with the relatively low incidence of adhesive dermatitis. Only two subjects were found specifically sensitive to adhesive plaster among 275 persons tested routinely at random. The five other subjects were known cases and not selected from among this group. Furthermore, the work herein reported covered a period of nearly five years, and the fact that the present investigator was in search of individuals who were sensitive to adhesive plaster was generally known to physicians and nurses in the hospital. It was also my impression that about one in six or more persons showed some form of irritation from adhesive plaster due to nonspecific factors. These factors were distinctly variable, as was pointed out in a summary above.

Bloch, quoted by Siemens[3] cited a frequency of adhesive dermatitis of one in 200 normal persons. No mention was made as to what was implied by the term dermatitis. He also stated that one subject among 100 cases of eczema was sensitive to plaster. Unna[8] tested a group of 100 persons, 4 per cent showing irritation, of whom two showed a strong reaction 4° to 5° (Bloch).

Van Cleve[11] tested 105 unselected patients in the dermatology wards of the Cleveland City Hospital with squares of adhesive plaster and with orris root. All tests were negative at the end of 24 hours, and after one week. Schwartz and Peck[12] studied 120 employees of a plant manufacturing adhesive plaster. Fifty showed a reaction to adhesive plaster at the first reading (48 hours) and 13 more at the second reading (96 hours). An incidence of 63 among 120 subjects is considerably higher than has been reported by other workers. Several clinical observers have pointed out that such a high incidence, if it were true of the general population, would create a problem of major medical importance (Woods[15] and Wright.[16]).

Specific Etiology.—The results of testing in the seven cases here reported revealed positive reactions to rosin in all seven cases and to rubber in three. All other ingredients gave negative tests. Siemens[3] reported reactions to various resins in his three cases. Van Cleve[11] tested two clinically sensitive patients with orris root and found both to react positively. The technic employed was not given, nor was testing carried out with any other substances. Schwartz and Peck[12] tested 21 subjects of the 63 who reacted to adhesive tape (6 immediate reactors, 12 delayed reactors, and 3 negative reactors), employing the following substances: starch, lanolin, orris root, I-rosin, olibanum, beeswax, gutta

siac, burgundy pitch, zinc oxide, and wood rosin. They did not state what mode of application was employed, nor in what state these ingredient substances were used. The tests were applied for forty-eight hours, the sites examined, and again inspected seventy-two hours later. One subject showed a generalized reaction making it impossible to read individual tests. Thirteen gave positive results as follows: wood rosin 8, pitch 8, I-rosin 6, rubber 5, beeswax 2, olibanum 2, orris, lanolin, and gutta siac 1. Seven gave no reactions.

It is difficult to reconcile the results of Schwartz and Peck[12] with those given in this communication. Their findings represent an incidence of 14 hypersensitive cases (by surface test) out of 21 subjects who reacted to adhesive plaster. On such a basis it should seem almost impossible to employ adhesive plaster either clinically or as part of the routine patch test. This does not coincide with general clinical experience. An editorial in the *Lancet*[17] in comment on the results of these authors, while admitting the frequency of adhesive plaster irritation, states that most cases are negligible and only a few cases are traceable to allergic sensitiveness.

It is also hard to explain this high incidence of test sensitivities in view of the fact that among adhesive plaster employees a clinical sensitization is uncommon. It was not possible for me to collect more than seven sensitive cases over a period of nearly five years. (This communication has been purposely delayed in the hope that more cases for testing would be available. However, recent discussion in the literature of the problem of adhesive dermatitis has prompted its publication at the present time.)

I am unable to analyze the findings of Schwartz and Peck because they do not give the details of their technic. They do not specify the state of the substances applied, nor the type of patch test used. Their patient who showed a generalized reaction to all tests may have been sensitive to the patch test itself. Moreover, the duration of application of the test substance in their series was forty-eight hours. The advisability of such a long period of application is a debatable point. Thus, in view of these unknown factors, any or all of which may to a certain degree explain the high incidence of positive reactions, a proper evaluation of their results becomes most difficult.

SUMMARY

Irritation from adhesive plaster (dermatitis) was unrelated to a family history of allergy, to the previous use of adhesive plaster, to dermographism, to the ability of the skin to tan, to the color of the eyes, or to the shade of the skin. Young adults reacted more readily than did older subjects, and females showed a greater tendency to react. Subjects did not react to the same extent at all times, and it did not seem possible to

group them according to degrees of reactivity. About one in six normal subjects showed some phenomenon of irritation, by far the greater number showing only an erythema.

Adhesive plaster dermatitis was of two types: (1) nonspecific and (2) specific. Both showed evidence of a dermatitis, though the former was less prone to show edema, vesicles, and desquamation. The nonspecific type was of shorter duration than the specific, and its effects were gone in a few days. There seemed to be an interplay of mechanical factors, such as tension, friction, maceration, skin infection, and capillary breakdown in the causation of nonspecific dermatitis.

In the specific variety there was a more lasting dermatitis of the type venenata, and positive reactions by the surface or patch test to one or more ingredients in the adhesive plaster were obtained. Only two specifically sensitive subjects were found among 275 normals tested with adhesive plaster. Five known cases of adhesive dermatitis were also tested. The results showed all seven to be sensitive to rosin and three also to native rubber. There was a fluctuation in reactivity to these test substances. In addition four of the subjects showed positive reactions to cellophane of the moisture-proof variety.

Specific adhesive plaster dermatitis seemed to occur in persons with a dermatitis due to other contact excitants. The person with a true sensitivity usually volunteered the information that he could not tolerate the application of adhesive plaster.

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DISCUSSION

DR. MATTHEW WALZER, Brooklyn.—I have watched Dr. Grolnick work on this problem for the last five years. The fact which most impressed me was that it was so difficult to find genuine adhesive dermatitis cases. In five years we found only seven.

It is a little bit difficult to reconcile this with the findings of Peck and Schwartz, who recently reported that about one-third of the cases which they tested showed positive reactions to adhesive. Dr. Grolnick found only 1 per cent. Unfortunately, Peck and Schwartz give very little detail concerning the type of cases which they tested or the technic which they employed.

It is stated that their series consisted of workers in a firm which manufactures adhesive plaster. This may account for the large number of positives which they obtained. At any rate, the difficulty which we encountered in evaluating their results demonstrates how necessary it is that writers reporting on patch testing give their technic in detail.

Patch testing is not a uniform procedure. There are many variables: first, in the amount of test material used, its concentration and form; second, in the duration of contact with the skin; third, in the nature of the covering material; fourth, in the interpretation of reactions; and so on. All these factors are important in evaluating the results of testing.

I am not making a plea for uniformity in technic, because, as Dr. Grolnick has shown, it is virtually impossible to get one technic that will work in every case. For that reason it is most advantageous to have several different technics available so that, regardless of handicaps, there will be at least one which will not irritate the skin in any given case. This is an important prerequisite in patch testing. It is virtually impossible to test adhesive plaster dermatitis cases using a patch test in which adhesive plaster is the covering material, as the irritation around the periphery of the patch destroys the results of the test itself.

I think Dr. Grolnick's contribution is decidedly important at this time in helping us to obtain a proper perspective of the relative frequency of contact dermatitis and of the difficulties which are encountered in the proper interpretation of tests on this type of case.

DR. A. F. COCA, Pearl River, N. Y.—I want to report one case of plaster dermatitis that illustrates the discouragement that you may have in looking for some substitute for the usual plaster. A colleague of mine was so sensitive to the ordinary adhesive plaster that his surgical operations were in themselves less troublesome than the large areas of denuded skin that he suffered after the operation on account of the blisters caused by the adhesive. For this reason I obtained for him a new nonallergic plaster to which, by test, he had been shown to be not sensitive.

He went for his next operation, having this on him for some weeks without the least difficulty. Then, two or three months later, I repeated the tests on him to make sure that the reactions were just as they had been before, but this time the test came out negative to the old plaster and positive to the new. In other words, he had lost his sensitivity to the old plaster and had developed a sensitivity to the new one.

DR. GROLNICK.—The point that Dr. Coca brings out struck me between the eyes often enough in that there was a marked variation in the extent of reactivity of the skin over a period of years. I mean, the patient

would at one time show a strongly positive reaction to a resinous ingredient, and three or four months later one would have to look for it. On repetition of the test, the thing would appear again. As you recall, one of the patients showed a severe adhesive dermatitis at one time and later he was able to tolerate the same plaster.

There are two types of cellophane used in the patch test. The moisture-proof cellophane used unknowingly may produce a positive patch reaction.

I found an incidence of 1 per cent of specific sensitivity. I should say that we ought not to quote percentages unless several thousand apparently normal persons have been tested.

Certainly, I should like to reiterate that some plea should be made for a standardization in the technic of patch testing.

USE OF BLISTER FLUID FOR PASSIVE TRANSFER SKIN TEST*

SALVATORE J. PARLATO, M.D.
BUFFALO, N. Y.

IN A recent publication, Spain and Newell[1] reported specific skin sensitizing antibodies in blister fluid which had been produced by the application of commercial cantharides plaster. They quoted other workers who, using similarly obtained fluid, were able to transfer skin sensitiveness to substances chiefly of nonprotein nature. There has not been reported any study of the reagins in the fluid content of blisters which have been sustained by burns. It would appear that localized heat which is severe enough to destroy considerable part of the epidermis would effect some alteration in the transudate which immediately forms on the affected site. One might expect some loss of antibodies of this fluid. This is not apparently true as far as the ordinary immunologic substances are concerned.[2] H. G. Wells[3] stated that immune bodies, complement, agglutinins, and antitoxins are present in the effusions in the skin which are caused by burns. This present study was undertaken for the purpose of determining whether the fluid contents of burn blisters contained skin sensitizing antibodies and whether they may be comparable to the reagins of artificially produced blisters and those of the blood serum.

A patient (Miss I. R.) aged twenty-one years, with symptoms of perennial coryza and asthma, recently had an accident in school, spilling some hot syrup on her right hand. Within an hour she came to the office for routine skin tests when it was noted that several large bullae had formed on her hand. Using aseptic precautions, about 2 c.c. of a light straw-colored fluid were obtained. Shortly afterward, 0.1 c.c. of the fluid, undiluted, was injected into each of three sites in the arms of two nonallergic persons (S. J. P. and J. A.). Twenty-four hours later, the three sites were tested with extracts of cat, dog and horse epithelia to which she was known to react positively both intradermally and clinically. The sensitized sites promptly gave positive reactions while the controls were negative. On the following day, two of these sites were tested with ragweed and chocolate extracts. Results of these tests are shown in Table I.

An attempt was then made to determine whether the reagins of the burn blister fluid could be exhausted. One of the sensitized skin sites of one of the receptors (S. J. P.) was given repeated injections of cat

*From the Department of Allergy, Columbus Hospital.
Read before the Society for the Study of Asthma and Allied Conditions, Atlantic City, May 2, 1936.

TABLE I

RESULTS OF TESTING SKIN SITES, SENSITIZED WITH BURN BLISTER FLUID AS COMPARED WITH ARTIFICIAL BLISTER FLUID AND BLOOD SERUM OF PATIENT I. R.

EXTRACT TESTED	DIRECT SKIN TEST	BURN BLISTER		ARTIFICIAL BLISTER		BLOOD SERUM	
		RECEPTOR		RECEPTOR		RECEPTOR	
		S. J. P.	J. A.	S. J. P.	K. R.	S. J. P.	K. R.
Cat ep. 0.001	+ + + +	+ + + + (Mkd)	+ + + + (Mkd)	+ + + +	+ + + +	+ + + +	+ + + +
Dog ep. 0.01	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +
Horse ep. 0.01	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +
Ragweed 0.01	+ +	Negative	Negative	Negative	Negative	Negative	Negative
Chocolate 0.1	+ + +	Not done	Negative	Negative	Not done	Not done	Negative

Controls were negative.
Decimals = mg. of nitrogen per cubic centimeter.

TABLE II

COMPARATIVE RESULTS OF DIRECT SKIN TESTS AND PASSIVE TRANSFER TESTS USING ARTIFICIAL BLISTER FLUID AND BLOOD SERUM OF FOUR ALLERGIC PATIENTS

PATIENT J. G.	RAGWEED 0.01	ORRIS 0.01	MILK 0.01	EGG WHITE 0.001	ALMOND
Direct skin	+ + + + (Mkd)	+ +	+ + +	+ +	+
Blister fluid	+ + + + (Mkd)	Negative	+ + + +	Negative	Negative
Blood serum	+ + + + (Mkd)	Negative	+ + +	Negative	Negative
PATIENT B. O.	**RAGWEED 0.01**	**HORSE EP. 0.01**	**SHEEP WOOL 0.01**	**EGG WHITE 0.001**	**CHOCOLATE 0.1**
Direct skin	+ + + +	+ + + +	+ + + +	Negative	+ + +
Blister fluid	+ + + +	+ +	+ + + +	Negative	+ + +
Blood serum	+ + + +	+ +	+ + + +	Negative	+ + + +
PATIENT H. K.	**RAGWEED 0.01**	**ORRIS 0.01**	**DOG EP. 0.01**	**RABBIT EP. 0.01**	
Direct skin	+ +	+ + + + (Mkd)	+ + + +	+ + +	
Blister fluid	+	+ + + + (Mkd)	+ + +	+ +	
Blood serum	+	+ + + + (Mkd)	+ + +	+ +	
PATIENT I. R.	**RAGWEED 0.01**	**HORSE EP. 0.01**	**DOG EP. 0.01**	**CAT EP. 0.001**	**CHOCOLATE 0.1**
Direct skin	+ +	+ + + +	+ + + +	+ + + +	+ + +
Blister fluid	Negative	+ + + +	+ + + +	+ + + +	Negative
Blood serum	Negative	+ +	+ + + +	+ + + +	Negative

Controls were negative.
Decimals = mg. of nitrogen per cubic centimeter.

epithelia extract. Within two days, there occurred a reduction and then a lack of reactivity not only to the 0.001 but also to the 0.01 solution. At this point, the site was tested with horse epithelium producing a positive result, indicating that the exhaustibility of the antibodies was specific. After a rest of eleven days, the same site reacted to the cat hair extract 0.01 solution.

Employing the technic of Spain and Newell, namely, the application of cantharides plaster for five to six hours on the anterior surface of the thighs, nearly 2 c.c. of blister fluid were obtained. About the same time, blood was withdrawn from the patient's arm, serum was separated and then sterilized by Seitz filtration. Four and five sites on skin of receptors (S. J. P. and K. R. respectively) were injected with 0.1 c.c. of the serum and like number of sites with 0.1 c.c. of the blister fluid. On the following day these sites were tested, the results being shown in Table I.

To corroborate further the work of Spain and Newell and to add to their series of cases in which reagins were demonstrated in blister fluid, three other adult patients under current study were selected from the allergy clinic of the Columbus Hospital. The first one (J. G.) has all-year asthma and eczema and ragweed pollinosis; the second (B. O.) has perennial asthma and ragweed pollinosis; the third (Mrs. H. K.) has bronchial asthma throughout the year with aggravation during the summer months. Artificial blisters were produced as described above. Blood was obtained and serum was separated during the same day. Seitz filtration was used. Skin sites in nonallergic persons were made simultaneously with the blister fluid and with the serum. Twenty-four hours later, all the sensitized sites were tested at the same time. The results as shown in Table II agree with those obtained with burn blister fluid and with the results reported by Spain and Newell.

CONCLUSIONS

1. Specific skin sensitizing antibodies have been found in the fluid content of a burn blister. Tissue changes and even destruction which are caused by burns do not seem to effect any loss of atopic antibodies.

2. The reagins in burn blister fluid further manifest the phenomenon of exhaustibility of reaction in sensitized site, being similar to that of the blood serum reagins.

3. The work of Spain and Newell on the reagin content of artificially produced blister fluid has been confirmed.

4. In some carefully selected cases, the artificial blister fluid could be used for performing the Prausnitz-Küstner test.

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DISCUSSION

DR. W. C. SPAIN, New York City.—I believe Dr. Parlato will agree with me that this finding has more of an academic than a practical value. It is hard to see that we would ever really need it in a practical way, because the blood serum is usually more easily obtained. In any patient in whom one could not obtain serum for transfer study because of a thickened eczematous skin, it would be difficult to obtain blister fluid also. It is conceivable that in an occasional infant one might use it, although a point must be emphasized that Dr. Parlato did not bring out, and that is that where there is a blister there is a pretty sore spot, whether it is produced accidentally with heat or purposely with cantharides plaster. In any case, one will have a patient who does not like the blister, or its effects, particularly when it is intentionally developed.

DR. PARLATO.—I appreciate Dr. Spain's remarks very much. It did occur to me, however, that the practicability of this test could be put to use by members of the Society who treat a large number of children. It has been my experience that mothers often dislike and even refuse to have blood drawn from the veins of their children for passive transfer tests. This procedure is not altogether a simple one, nor always successful. An easier and quicker method for performing a few indirect skin tests would do much to retain the cooperation of both the child and the mother.

I brought in this paper with the hope that our pediatrician friends would try it and then report later.

THE RELATIVE MERITS OF SEASONAL AND PERENNIAL TREATMENT OF HAY FEVER*

ALBERT VANDER VEER, M.D.
NEW YORK, N. Y.

WHILE the dispute over the relative merits of seasonal versus perennial treatment of hay fever will probably never be settled any more than we shall eventually agree upon the scratch or intradermal methods of testing, it seems timely to present any evidence we may have bearing on one side of the question or the other.

Chart I shows the results in a group of late hay fever patients treated with ragweed injections over a period of five years from 1930 to 1934 inclusive. The number of patients varied from 385 in 1933 to 499 in 1930, averaging about 430 per year. Of these about 75 per cent answered the questionnaire sent to them at the end of the season. Satisfactory results include the usual three-plus and two-plus groups, or roughly from 75 to 100 per cent protection. In 1930 and 1931 about 10 per cent were being treated perennially, the rest receiving seasonal treatment; while in 1932, 1933, and 1934 the perennial group had risen to 30 per cent.

The center line of Chart I gives the percentage of satisfactory results for the whole group, the upper line for the perennially treated cases, and the lower line for those treated seasonally. It can be seen very clearly that the perennial results are uniformly better than the seasonal results by from 8 to 10 per cent. This would seem to settle the matter conclusively if one relied implicitly on statistics. It is always well, however, to investigate how any statistics are obtained. In the present case we would point out that if a patient has done well with his hay fever treatment, it is relatively easy to persuade him to continue his injections throughout the year, while a patient who has done badly is likely to become discouraged and discontinue treatment entirely or at least drop it when the season is over and begin again in the spring. This factor alone would tend to place more of the satisfactory cases in the perennial group, but the exact number is not ascertainable.

There are two decided disadvantages in the perennial treatment. Many patients forget to take their injections regularly, and, if the elapsed interval is five weeks or more, the risk of inducing a constitutional reaction is decidedly increased. The dose must be decreased and then worked up again at weekly or two weekly intervals, increasing the number of injections to approximately the same as in the seasonal treat-

*Read before the Society for the Study of Asthma and Allied Conditions. Atlantic City, May 2, 1936.

ment. The second objection is that a fair number of patients apparently become saturated and develop constitutional reactions from much smaller doses than they have previously tolerated. When this condition occurs, it is necessary to stop all treatment for the winter and begin again in the spring with weekly injections. In general we have found that the percentage of constitutional reactions is about the same for both groups, namely, 13 per cent for the patients and 1 per cent for individual injections. We have an impression that perennial treatment is more likely to produce a permanent cure eventually, but we have no figures to substantiate this. With most patients the maximum dose of extract can be materially increased if injections are continued throughout the year,

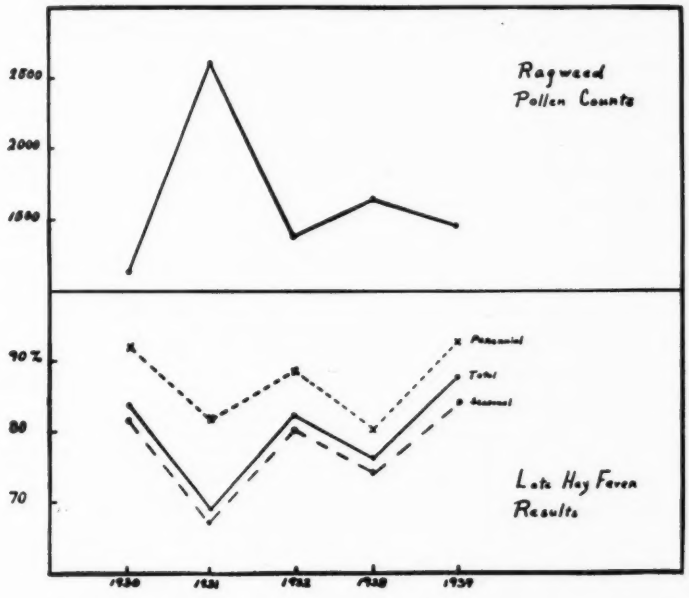

Chart I.

but with some there is apparently a limit of tolerance or ceiling, and any increase above this invariably results in a constitutional reaction.

Lastly, perennial treatment is better suited to those who have a hypersensitiveness to a single or at most two or three pollens, particularly ragweed and grass pollens. It is common knowledge that hypersensitiveness to the tree pollens is likely to change from year to year, and it is a little embarrassing after giving injections throughout the winter to retest the patient in the spring and find that he needs a different mixture and that this must be given once a week again to work up his dose of some new pollen to which he reacts.

In general we must conclude that the proper solution of the problem requires the use of both methods, choosing the right one for each patient according to the indications in his particular case.

Another point brought out by this chart is that the less pollen there is in the air during the season the better will be our results for that year and vice versa. This, of course, is a reasonable conclusion, but it is some satisfaction to have it shown so graphically. The top line shows the total ragweed count for each season from 1930 to 1934, and this line varies inversely with the percentage of satisfactory results. For instance in 1930, with a low total pollen count of 1,100, the satisfactory results reached a high of 80 per cent; while in 1931, with a total pollen count of 2,600, the percentage of satisfactory results fell to 69 per cent, and many of us remember the grief we suffered that year.

DISCUSSION

DR. C. G. WESTON, Glen Ridge, N. J.—The ideal in the perennial hay fever treatment is the establishment of a perennial resistance for that individual. This means a threshold resistance which will keep him free from symptoms even at the height of an extremely heavy pollen season.

The ideal is again approached by establishing an individual dose which can be given without fear of constitutional reactions at fairly long intervals.

These intervals with established doses vary considerably with the individual patients, often as long as two months without constitutional reactions.

DR. MILTON B. COHEN, Cleveland.—I have been impressed with the advantages of the perennial management of allergic patients, not necessarily the perennial injection of the ragweed hay fever patient.

Another point to be considered, however, when one tries to compare the results of preseasonal and perennial treatment, is the fact that when the patient is coming to your office at reasonably regular intervals after the season, you find out a lot of things about him that you did not know before, and you take care of many minor allergic things which he has bothering him. Consequently, one gets, in the end, a better result; whether because of total effort along allergic lines, or because of effort in getting more prolonged ragweed treatment, I do not know.

I do think, however, that Dr. Vander Veer has made a very nice point, at least has alluded to it, when he says that you cannot treat them all any one way. We never are going to get to the place where we can set up some kind of routine schedule and fit the patient to the schedule. We are always going to have to individualize treatment, and there will always be some patients who cannot be treated one way, and there are always going to be patients who will seldom have a systemic reaction no matter what you give.

DR. SELIAN HEBALD, New York City.—Dr. Vander Veer's résumé is interesting, his experience is so large.

I think that in a general way larger dosage means better protection. If you add the total amount of extract given to a patient treated perennially, you will find that it is more than the amount you have given to a patient treated seasonally. I believe that the better result which is obtained in perennial treatment is due at least in part to this quantitative difference.

DR. FRANCIS M. RACKEMANN, Boston.—I want to ask whether there is evidence that the perennial method leads to permanent results more rapidly than does a series of preseasonal treatments.

DR. W. T. VAUGHAN, Richmond.—I should like to ask Dr. Sherman what Dr. Vander Veer means by "seasonal" treatment, whether he means entirely the preseasonal treatment, or whether there are also some coseasonal cases in the series.

DR. HARRY MARKOW, Brooklyn.—I should like to ask Dr. Vander Veer whether, when he varied the frequency of the treatments during the active season, from one to two, three or four injections during the month, he observed any difference in clinical results.

DR. SHERMAN.—I do not know whether I can answer all questions. I am pretty sure that there is no postseasonal treatment in the figures. I believe the seasonal treatment means preseasonal.

Probably Dr. Cooke can answer the other questions much better than I could answer them.

DR. ROBERT A. COOKE, New York City.—I am sure that when Dr. Vander Veer says "seasonal" treatment he means not only pre- but coseasonal, in which treatment is begun before and is continued throughout the season. That is the usual routine.

The perennially treated patients are given injections usually once every month, but there are a few in whom the injections cannot be allowed to go four weeks. In those few instances injections may be given at three-week intervals, or possibly at two. That is rarely so.

Whether the injections should be increased in frequency during the season or not, again depends upon the individual. By and large, we try to have them take the injections only once a month, but there is also the alternative given to them that if during the season they have any severe or definite attacks of hay fever at that time, they may, after an interval of a week, take an extra dose. In many of these cases, in fact, I think in most of them, this is not done. These patients often go through the season perfectly.

The question of the permanency of cure is an extremely difficult one. Dr. Vander Veer, I think, covered that as well as we can possibly state at the present time. There is no definite evidence that the cure is permanent, but we feel that it probably is. In other words, today we discharge as "apparently cured" a greater number of patients who have been under perennial treatment than we ever did heretofore on seasonal treatment. Our statistics, which of course have not gone yet over very many years, indicate that these patients are holding up, so to speak, and that ultimately a number of them seem to lose their skin reactivity.

SKIN HYPERSENSITIVITY TO MOLDS

An Attempt to Correlate This with Clinical Allergy*

Robert W. Lamson, Ph.D., M.D., and Erving L. Rogers, M.D.
Los Angeles, Calif.

THE importance of house dust as an excitant in allergic conditions is widely recognized. The active agent is not always easy to identify; in fact, Cooke[1] in his early work was unable to correlate it with sensitization to any known constituents of the dust. Not a few patients react to their own house dust, but to no "stock" allergens. Storm van Leeuwen was one of the first to suggest that microorganisms, especially molds, were important allergic substances in dust. He explained the freedom from asthma in one locality on the basis that molds were absent, or nearly so, from that atmosphere. He has reported experimental evidence that *Aspergillus fumigatus* and a *Penicillium* produced anaphylactic symptoms in guinea pigs on second inhalation.

Since 1924 these and several other molds have been implicated. Walzer[2] discussed several reports in some detail and evaluated the evidence for and against a true atopic mechanism. Brief excerpts from these will be given, and the reader is referred to Coca's[2] book and other reviews for the details. Cadham[2] cited three cases of asthma from spores of wheat rust. Van Leeuwen[2] apparently showed that *Aspergillus fumigatus* is a common infester of kapok. Walzer[2] employed van Leeuwen's extract of this fungus. In one patient of his series of 14, there was a reaction, and this seemed of little significance. Hansen[2] found 15 per cent of his group positive to molds. The species were: *Aspergillus glaucus, A. fumigatus, A. nidulans,* and in one instance *A. niger* (from a cat's fur), and *Penicillium "glaucum."* Bernton[2] tested 125 patients with 13 molds. One only was sensitive, and this to *Aspergillus fumigatus:* an incidence of 0.8 per cent. Hopkins and his coworkers[3] reported asthma and eczema from *Alternaria.* Walzer[2] found evidence in these several reports against the usual atopic phenomena.

Rackemann,[4] in his book, gives little space to a consideration of molds in allergy; although he appears to accept Hopkins'[3] proof that a mold was the etiologic factor in asthma. Flood[5] used an *Alternaria,* two *Aspergilli, Mucor plumbeus* and a *Penicillium,* and found that 8 (of 44) patients, 14 per cent of his series, gave positive skin reactions. Typical asthmatic attacks were produced in one of these by spraying the nose and throat with a filtrate of *Mucor plumbeus,* one of the fungi

*The patients represented in this study were from the allergy clinics of the Los Angeles County General Hospital, the Santa Fe Hospital Association, the Eye, Ear and Throat Hospital, and a few from private practice.

to which the patient gave a positive skin test. Balyeat[6] found less than 1 per cent (of 480 patients) mold sensitive. Brown[7] employed the most extensive list of molds yet reported: 68 species. He discussed 24 illustrative cases which gave positive reactions. In 1932, Towey and his associates[8] published a comprehensive study of 35 patients presenting symptoms of asthma associated with the inhalation of the spore dust of *Coniosporium corticale* from maple bark. Approximately one-third (of 32) of those most heavily exposed, for more than two months, developed asthmatic symptoms. These gave positive skin reactions to an extract of this dust. Reagins could not be demonstrated. Berton and Thom[9] reported a study of 8 patients who were tested with several molds, and each reacted to *Alternaria* or a *Trichophyton* or both. Three (37.5 per cent) reacted to no other allergen, and five reacted to other allergens. Credille[10] obtained a positive skin reaction to an extract of *Aspergillus fumigatus*, and he was led to believe that this was of etiologic significance. Forty-three additional asthmatic patients were tested, with negative results. Prince and his associates[11] isolated 29 different cultures of molds and tested these on 18 individuals; four of these were normal persons and negative. Two patients with asthma and one with hay fever were also negative. The remaining 11 patients gave positive skin tests; although the authors considered these of etiologic significance in but 8 patients.

Feinberg[12] tested 243 patients, by the scratch method only, to 12 molds; and 22.6 per cent of his patients reacted to one or more. In an additional 11 per cent he demonstrated skin sensitivity to yeasts only. His list of molds includes the species we employed and possibly the source was the same.

We wish to report a somewhat larger series than any mentioned above; namely, 702 males and 557 females. Each of these 1,259 patients was tested with extracts of nine different molds,* and 154 patients (12.2 per cent) of the total series reacted to one or more. The methods employed and an analysis of the results will be given in succeeding paragraphs.

One gram of each mold powder was extracted at room temperature for 48 to 72 hours in 50 c.c. of neutral (pH 7.4) isotonic phosphate buffer solution, containing 50 per cent of glycerin. The extract was shaken several times each day and at the end of the extraction period was filtered through a Seitz filter. The 1:50 extract was then diluted 20 times with sterile salt solution to a final concentration of 1:1,000 and this was used *intracutaneously* for all tests.

The patients were under the personal supervision of one of us (L.), and a period of approximately three years was required to accumulate the data. The patients might be divided into four groups, depending

*The following mold powders, obtained from the Arlington Chemical Co., were employed in this study: *Alternaria* spp., *Aspergillus fumigatus, Aspergillus glaucus, Aspergillus nidulans, Asperaillus niger, Chaetomium* spp., *Monilia* spp., *Mucor plumbeus,* and *Penicillium chrysogenum.*

upon their clinic or other source. This has been done in Table I, and the proportion of each group to the total has been indicated in the first column. In passing, it might be noted that but 20.5 per cent represent private cases. It seemed of interest to determine the ratio of the positives in each of the four groups to the total number of patients of that group. Identical standards of determining a positive reaction were employed in all the clinics. None was called positive that did not have at least one pseudopod. The remainder of Table I gives the distribution of mold-positive and mold-negative patients from the four sources, and these are further subdivided on the basis of sensitivity to other allergens as explained in the footnote.

It was found that 13.5 per cent of the males and 10.6 per cent of the females gave positive reactions to one, or more, molds; the average of positive reactions for the entire series is 12.2 per cent of the patients. The several clinic groups show a wide variation in the percentage of patients found sensitive. The first group had 40.6 per cent mold-sensitive patients, the second 5.9 per cent, the third (private cases) 27.2 per cent and the final one 12.8 per cent.

Table I shows that 154 patients were mold sensitive, and that all but 21 of these reacted to other allergens. Incidentally it may be noted that approximately 52 per cent of the total series reacted to other allergens; of these, 259 were of the second clinic group (only 35 per cent of its total), while in the Santa Fe group 167 patients (85 per cent) were sensitive. The possible significance of these in comparison with mold sensitivities will be discussed.

TABLE I

SKIN REACTIONS TO MOLDS IN 1,259 PATIENTS

CLINIC	PATIENTS		MOLD POSITIVE				MOLD NEGATIVE			
			OTHERS* POSITIVE		OTHERS NEGATIVE		OTHERS POSITIVE		OTHERS NEGATIVE	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
E. E. N. T. Hosp.	32	2.54	13	1.0	0	0.0	17	1.35	2	0.16
L. A. C. G. Hosp.	774	61.47	32	2.5	14	1.11	227	18.03	501	39.79
R. W. L. Private	258	20.50	63	5.0	7	0.55	133	10.52	55	4.37
Santa Fe Hosp.	195	15.48	25	1.9	0	0.0	142	11.28	28	2.22
Totals	1259	99.99	133	10.4	21	1.65	519	41.18	586	46.54

*"Others" refers to a list of tests used as a routine which includes pollens, foods, epidermals and, in a few instances, the patient's own house dust.

In the following tables data relative to the 154 (12.2 per cent) mold-positive patients are presented from several points of analysis. A preliminary study of these data indicated that reactions to *Alternaria* exceeded those for any other mold. The next two most frequent reactions were to *Chaetomium* and *Aspergillus fumigatus* respectively. These findings led us to arrange the reactions into four groups as indicated in the column at the left of Table II.

TABLE II

SUMMARY OF TOTAL MOLD REACTIONS IN 154 PATIENTS

NUMBER OF REACTIONS TO THE FOLLOWING	NO. OF PATIENTS REACTING	DISTRIBUTION OF SKIN REACTIONS TO ONE OR MORE MOLDS									TOTAL NUMBER REACTIONS	NUMBER OF PATIENTS REACTING
				ASPERGILLUS								
		ALTERNARIA SPP.	CHAETOMIUM SPP.	FUMIGATUS	GLAUCUS	NIDULANS	NIGER	MONILIA SPP.	MUCOR PLUMBEUS	PENICILLIUM CHRYS.		
Alternaria alone or with others	20 46	66	31	23	15	18	7	8	10	12	190	66
Chaetomium alone or with others except Alternaria	7 17		24	5	3	2	4	4	3	6	51	24
A. fumigatus alone or with others except Alternaria and Chaetomium	3 9			12	4	2		1	1	3	23	12
Others except the first three groups	52				10	13	11	6	15	14	69	52
TOTALS	154	66	55	40	32	35	22	19	29	35	333	154
Per cent of total mold reactions		20	15.9	12	9.9	10.5	6.6	5.7	8.7	10.5		
Per cent of patients reacting to molds		48.8	35.7	26	20.7	22.7	14.3	12.3	18.9	22.7		

In the first group 20 patients reacted to *Alternaria* alone, and only two additional ones reacted to eight of the nine molds. In the second group seven reacted to the key mold alone, and no other patient reacted to more than four molds. In the third group the maximum number of mold reactions on any one patient was three. The final group contained 69 reactions on 52 patients, an average of 1.2 molds per patient.

The totals show the number of positive mold tests (a total of 333), but they cannot show the number of patients. In many instances the same patient reacted to many different molds. Where but one mold reacted on a patient, those data represent patients as well as an identical number of reactions.

It seemed desirable to determine, in these mold-sensitive individuals, the frequency distribution by hemidecades, and this is recorded in Table III. For each age group we have indicated whether or not the patient reacted to stock allergens. Table III also indicates the clinical conditions emphasized by the patient. Nasal conditions, whether alone or combined with chest symptoms, include the complaint of frequent head colds and on through the list to typical pollinosis. Chest symptoms also vary widely. Nasal and chest symptoms occur together much more frequently than either alone. Only four patients are classed under "skin": these presented symptoms of eczema, urticaria or angioneurotic edema without other allergic manifestations. It is interesting to note that in the mold-sensitive group, the hemidecades between 5 years and 14 years include about one-third of the patients reacting to other allergens; the number of non-sensitive patients (21) is of minor importance in the entire series (154 patients).

TABLE III

COMPARISON OF MOLD SENSITIVENESS AND LOCATION OF SYMPTOMS, BY HEMIDECADES, IN 154 PATIENTS

PATIENTS SENSITIVE TO MOLDS					LOCATION OF SYMPTOMS			
AGE IN YEARS	WITH OTHER ALLERGENS		ALONE					
	NO.	%	NO.	%	NOSE	CHEST	NOSE AND CHEST	SKIN
1 day to 4.9	4	2.6	0	0.0	0	0	4	0
5- 9	24	15.6	1	0.6	10	3	12	0
10-14	22	14.2	2	1.3	7	4	12	1
15-19	11	7.1	1	0.6	3	3	6	0
20-24	6	3.9	2	1.3	6	1	1	0
25-29	8	5.2	2	1.3	6	2	2	0
30-34	14	9.1	2	1.3	5	4	5	2
35-39	12	7.8	4	2.6	4	6	5	1
40-44	11	7.1	2	1.3	4	1	7	0
45-49	10	6.5	2	1.3	1	4	7	0
50-54	8	5.2	2	1.3	4	3	3	0
55-59	2	1.3	0	0.0	1	0	1	0
60-64	1	0.6	1	0.6	0	2	0	0
TOTALS	133		21		51	33	65	4

34.4% of these patients are less than 15 years of age.
74.7% are less than 40 years of age.

DISCUSSION

The preceding tables furnish data which may assist in establishing the significance of molds in allergy. We wish to emphasize that skin sensitivity alone is not proof of etiologic relationship. In this study it was impossible to carry out passive transfer experiments. Even had they been done and yielded negative findings it would not entirely exclude molds from the category of allergens.

When so large a series as 1,259 patients is tested, and yet but 12.2 per cent give positive reactions to one or more of the nine molds, it would appear that simple irritative phenomena are not conspicuous. It should be noted that the percentage of positives agrees rather closely with the figure of 15 per cent reported by Hansen, and that the data for private patients in this group agree with those more recently reported by Feinberg for his series. The series contains slightly more males (55.7 per cent) than females (44.3 per cent). The proportion of males reacting to molds (13.5 per cent) is slightly greater than that (10.6 per cent) among the females. If molds are important factors in house dust, one might suspect that a greater proportion of females would demonstrate sensitivity to them. Our results are such that no difference in mold sensitivity between the sexes can be claimed.

It seems logical next to consider the relationship of skin sensitivity to molds in patients already known to be hypersensitive to other allergens. The Santa Fe Clinic contains the greatest proportion of hypersensitive patients of any of the three major groups, yet the incidence of mold sensitivity is relatively low (12.8 per cent). Since the majority of these patients live on the desert, one may speculate whether the dry atmosphere contains a minimum of molds and hence the patients have not had opportunity to develop such a sensitivity. If van Leeuwen's theory were applicable to the County Hospital group, it would seem that a high percentage of mold sensitivity should be found. Some of these patients, representing the lower economic levels, live in the poorer sections of the city—usually in one-story dwellings where dampness and proximity to the soil should predispose to sensitivity. This clinic furnished 61.5 per cent of the entire series, and yet the lowest ratio (5.9 per cent) of mold sensitivities. This can be correlated with a low ratio of sensitivity to stock allergens, hence many of these patients are probably nonallergic.

Our findings tend to agree with those of other workers who have emphasized the frequency of skin sensitivity to *Alternaria, Aspergillus fumigatus* and *Chaetomium*. In fact when *Alternaria* reacted, it tended to include reactions to many of the other molds. Although the total number of reactions to each of three of the four species of *Aspergillus* is similar, no major antigen could be shown to exist within members of this genus. A significant number (13, or 37 per cent) of the reactions to

A. nidulans occurred in the absence of a reaction to *A. fumigatus.* Fifty per cent of the reactions to *A. niger* were likewise not correlated with a sensitivity to *A. fumigatus,* the most frequent reactor among the *Aspergilli.* The group of 154 mold-sensitive patients gave but 333 mold reactions, an average of 2.16 molds per patient. Twenty patients (30 per cent of 66) sensitive to *Alternaria* reacted to this mold alone. The next two in order of frequency of reactions, *Chaetomium* and *A. fumigatus,* reacted alone in but 12.7 per cent and 10 per cent respectively.

We were surprised to learn that 75 per cent of the mold-sensitive patients were under the age of forty years. This is doubly significant in view of the fact that the largest group of patients, County Hospital Clinic, has no one under twelve years of age, and that the Santa Fe group contained but three or four children: members of employees' families. Had the entire series contained the proportion of children equivalent to their incidence in the allergic population, we believe that more than 34.4 per cent of mold-sensitive patients would be found in the groups under fifteen years of age.

An investigation of those patients reacting only to molds, or in 11 additional instances to house dust, revealed no striking relationship to age, major complaint, sex, or other factor. In the house dust sensitive group, the evidence seems to be against van Leeuwen's claim of the importance of molds in determining skin sensitivity to dusts. These findings may be construed as evidence for the association of skin sensitivities to mold and of an allergic condition. This is supported by the fact that the entire group not sensitive to usual stock allergens contains but 21 patients—13.6 per cent of all mold-sensitive individuals; an apparent correlation with presumptive allergy in the remainder (86.4 per cent). In this connection, let us again note that none of our mold extracts reacted on 87.8 per cent of the 1,259 patients, many of whom we have never considered to have a true allergy.

Several of the molds we have used have been implicated in clinical medicine. The evident relationship of *Alternaria* to one case of asthma has been discussed. Many textbooks refer to *Aspergillus fumigatus* as a cause of certain pulmonary conditions and *A. nidulans* has been implicated in aural mycosis. The possible significance of one species of *Monilia* in sprue is well known. Two species of *Mucor* are said to develop especially in external cavities as nasopharynx and external ear. Each type we have employed may be found in the environment of certain patients, and it is conceivable that contact may result in development of skin hypersensitivity without engendering or even implying a clinical allergic condition. We have, however, shown the tendency to mold sensitivity in those patients already known to be allergic as compared to sensitivity in clinically doubtful or negative patients.

So far as our results of treatment are concerned, we feel that the evidence is still too meager to emphasize. Only a few patients have been

treated with molds alone. In one of these, mold reactions were obliterated by a total of 40 or 50 injections over a period of two years. In evaluating this or other similar type of treatment, one should deduct from his results the nonspecific benefit resulting from the injection of a foreign protein. This phase of the problem will receive further study.

SUMMARY

1. Skin hypersensitivity by intracutaneous test to a glycerin buffer extract of molds was detected in 12 per cent (154) of 1,259 patients. This alone does not establish etiologic relationship. The absence of reaction in the remainder seems to exclude simple irritative responses.

2. One hundred fifty-four patients tested with extracts of 9 species of molds gave 333 positive reactions; an average of 2.2 molds per patient. Of this group, 13.6 per cent reacted to no stock allergen. The Santa Fe group, representing 15.5 per cent of the total patients tested, showed an especially large proportion of true allergic conditions with accompanying pollen sensitivities. In spite of this, but 13 per cent of this group was mold sensitive. The possible significance of residence in a dry climate is discussed in this connection.

3. Molds previously suspected in allergic or other clinical conditions reacted most frequently in this series. *Alternaria* gave 20 per cent of all mold reactions, and 57 per cent of all mold sensitivities were included with it.

4. No major antigenic factor was noted among the results for four species of *Aspergillus.*

5. Sex seems to be no factor in mold sensitivity.

6. Seventy-five per cent of all mold-sensitive patients were less than forty years old, even though the entire series studied has a relatively low ratio of individuals under twelve years. The age of forty years is more or less a dividing point between true and pseudoallergic periods.

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Special Reports

HYPERSENSITIVENESS TO CELERY*

Report of a Case of Celery Dermatitis

H. Harold Gelfand, M.D.
New York, N. Y.

FREQUENT reports have been made in the literature regarding the occurrence of contact dermatitis. Investigations along this line constantly augment the already varied list of irritants[1] responsible for this affection.

Legrain and Barthe[2] have described a case of dermatitis caused by picking celery. The patient had been engaged in his occupation for a period of ten days, when he noticed the onset of an acute dermatitis, characterized by erythema, edema, and vesicles with a serous discharge. The eruption occurred on the dorsa of the hands, the posterior surface of the forearm, and also on the dorsal and lateral surfaces of the fingers. After he had desisted from picking celery for thirteen days, the condition cleared up, but on the following day when he scraped the roots of celery, the dermatitis recurred. The authors believed the condition to be due to the aromatic oil of celery and were impressed with the similarity of the condition described to that of parsnip illness, an erythematovesicular dermatitis, occurring in Belgium among the gatherers of cow parsnips. A form of dermatitis, confined to the upper extremities, was described by Henry[3] as having appeared among workers in three factories in which celery was prepared for canning during the autumn of 1932. Approximately 4 per cent of these workers were affected with the eruption. Their transference to another kind of work, combined with treatment, resulted in the complete cure of about 41 per cent of this group within the first week and 86 per cent within four weeks. Henry suggested that the main factor involved in this condition was limonene, contributing causes being exposure to water, friction and individual susceptibility.

CASE REPORT

H. S., aged thirty-five years, had been in the employ of a fruit company for two months, handling and washing their products, when he noticed the appearance of a rash on both hands. After consulting a dermatologist, he was advised to cease his occupation temporarily. Fol-

*From the Department of Allergy, the Roosevelt Hospital.
Read before the Society for the Study of Asthma and Allied Conditions, Atlantic City, May 2, 1936.

lowing a discontinuation of employment for five weeks, the condition entirely disappeared. When he again became engaged in his work for a period of four days, however, there was a recurrence of the eruption. At this time he came under our observation because of the severe lesions involving both his hands.

Fig. 1.—Eczema of hands caused by handling celery.

Fig. 2.—Patch test with root of celery.

In order to determine the causative agent, a series of patch tests were made during the period of time from March 19 to June 4, 1934, at varied intervals. The results were as follows:

1. Intradermal tests and patch tests with aqueous extract of celery were negative.

2. The juice, squeezed from celery stalks and passed through a Seitz filter, produced negative patch tests.

3. Patch tests with fresh ground celery root (Fig. 2) and celery leaves were positive.

4. The use of separate ethyl ether extracts of dried celery leaves and celery root resulted in positive patch tests, the latter giving the more severe reaction (Fig. 3).

5. The ether soluble portion of a steam distillate of celery root yielded strongly positive patch tests. Tests with the celery root residue following steam distillation were negative.

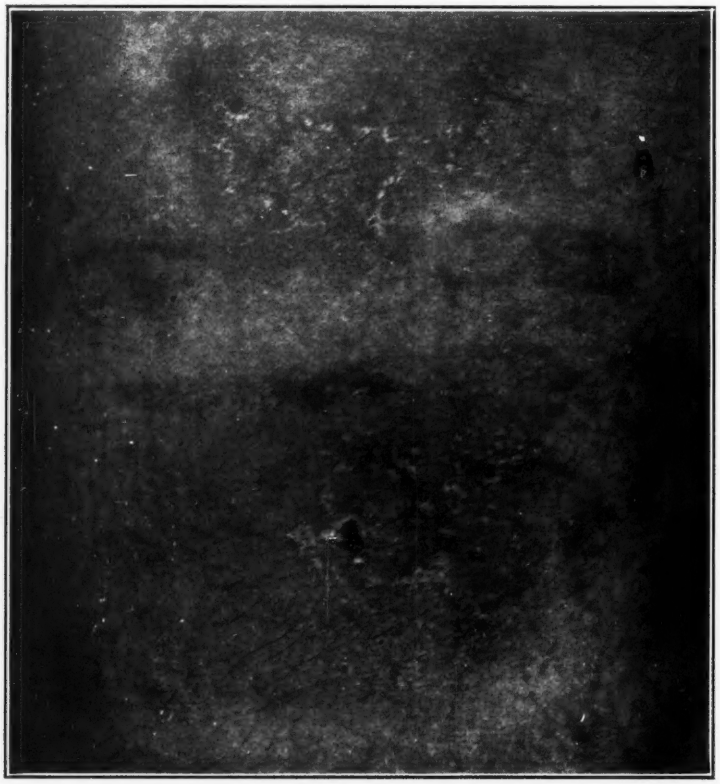

Fig. 3.—Patch tests with ether extract of dried celery leaves and celery root. *A*, ether extract of dried celery leaves; *B*, ether extract of dried celery root.

6. Commercial oils, derived from celery leaves and celery grains, produced positive patch tests equal in severity to those from the ether soluble volatile oil as prepared in our laboratory. The results from patch tests with oils in 1:100 dilutions of absolute alcohol were definitely positive. A 1:1000 dilution caused a slight itch but no objective lesion.

Convinced that the volatile oil of celery was the causative irritant, we gave the patient treatment similar to that employed for poison ivy. Celery oil in 1:1000 alcoholic dilution was initially employed because the application of this strength in a patch test barely produced a positive

reaction. The dosage was gradually increased from this point until a 1:10 dilution was reached. The patient showed good tolerance as long as the injections were given at intervals of one week. Occasionally when the interval between injections was extended, a severe local reaction resulted, which necessitated a diminution in the dosage and a readjustment to the usual graduated scale.

Following a course of injections of gradual increases in dosage of celery oil up to 1:10 dilution, the patient then resumed his original occupation and reported no further untoward effects, but refused to return for further studies.

CONCLUSION

A case of dermatitis of the hands was caused by the handling of celery. The irritant proved to be the volatile oil of celery.

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235 East Twenty-Second Street.

SENSITIVITY TO TAKA-DIASTASE (ASPERGILLUS ORYZAE)

Report of a Case*

Simon S. Leopold, M.D.
Philadelphia, Pa.

ALMOST without exception, writers on the subject of mold allergy in its relation to bronchial asthma and hay fever start with a survey of the literature, emphasize the ubiquity of these allergens, speculate on their specificity, attempt more or less convincingly to correlate reactions to fungi with sensitivity to dust, and append their case reports.

No such routine will be followed in this brief presentation. A complete bibliography will be found in Feinberg's[1] excellent report published just a year ago. The ubiquity of the molds, especially the *Aspergilli,* the *Penicillia* and the *Mucors,* as the "weeds of the culture room," (Thom and Church[2]) is acknowledged; their specificity and the part they play in dust sensitivity are still to be determined. The inevitable case report will be presented but only because sensitivity to *Aspergillus oryzae* (taka-diastase) is sufficiently uncommon to justify me in adding this substance as a matter of record to the ever growing list of allergens.

I have found two references to sensitivity to *Aspergillus oryzae.* Thom and Church[2] quote Oshina in a personal communication, the subject a manufacturer who experienced more or less vaguely defined irritation of the respiratory organs from contact with *Aspergillus flavus oryzae.*

Brown[3] tested 24 patients with molds and in two instances demonstrated cutaneous sensitivity to *Aspergillus oryzae.* In Case 1 of his series, this was one of 19 positive reactions to stock preparations and in Case 8, *Alternaria* and *Aspergillus oryzae,* recovered from mattress dust, were slightly or doubtfully positive.

CASE REPORT

Male, white, aged twenty-five years, was referred by Dr. Karl M. Houser on Oct. 16, 1935. He had had seasonal fall hay fever since the age of six years and bronchial asthma since the age of ten years. His asthma had been perennial for many years with more acute exacerbations during each fall pollinating season. No relief ensued from change of climate and environment. Pollen immunization for the past three seasons failed to influence either his fall hay fever or his bronchial asthma. He is a druggist by trade and stated specifically that he knew of nothing to which he is exposed in his occupation which appeared to provoke irritation of the respiratory tract.

Physical examination of the chest revealed an old rachitic deformity, moderate emphysema, and scattered sibilant râles. Clinical examination of the sinuses by

*Read by title at the Fourteenth Annual Meeting of the Association for the Study of Allergy, May 2, 1936.

Dr. Houser showed profuse purulent discharge in both nares. On transillumination the frontals were clear, the left antrum was clouded. X-ray examination by Dr. Pendergrass revealed bilateral mucous membrane thickening of the ethmoids, mucous membrane swelling of both maxillaries and of the sphenoids. X-ray examination of the chest showed moderate emphysema and the usual intensification of hilum and trunk shadows observed in long standing bronchial asthma.

Routine sensitivity tests revealed strongly positive reactions to many pollens, stock dust, several animal epidermal proteins, and numerous nonessential foods.

On October 23, one week after his initial visit, the patient volunteered the information that four days previously he experienced a violent asthmatic attack which occurred abruptly while he was compounding a prescription containing

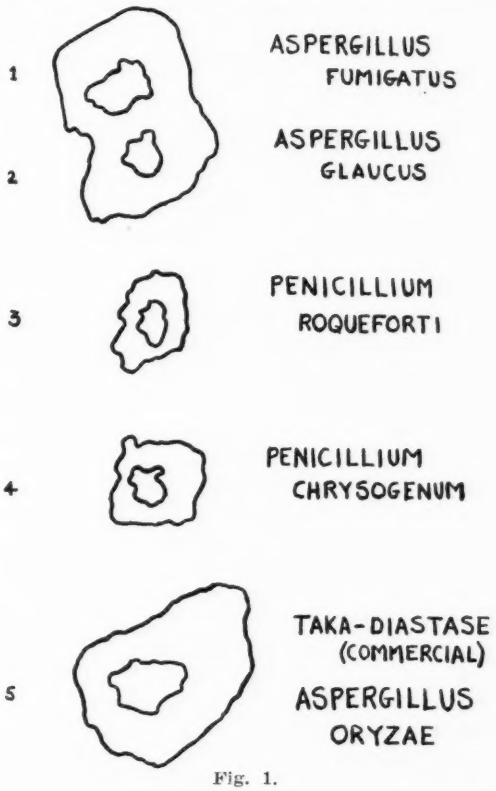

Fig. 1.

powdered taka-diastase and powdered theobromine sodium salicylate. He then recalled that he had had a precisely similar attack while compounding this same prescription on October 12. He was instructed to submit the two drugs used. A scratch test with theobromine sodium salicylate was negative. Commercial taka-diastase by similar method produced a strongly positive reaction with an irregular wheal 2.2 cm. by 1.6 cm. and a surrounding zone of erythema 5.7 by 4.4 cm. in diameter.

Cutaneous tests were then made with the following molds and yeasts: *Aspergillus fumigatus, Aspergillus glaucus, Aspergillus niger, Penicillium roqueforti, Penicillium chrysogenum, Penicillium camemberti, Mucor plumbeus, Alternaria, Monilia,* yeast from oysters, Fleischman yeast, baker's yeast, brewer's yeast, distiller's yeast, lactose fermenting yeast, and lager beer yeast. Definitely positive reactions were obtained

with *Aspergillus fumigatus, Aspergillus glaucus, Penicillium roqueforti,* and *Penicillium chrysogenum.* None of these were as large as the reaction obtained with commercial taka-diastase.

A specimen of sputum was collected under sterile precautions and submitted to Dr. Forrester of the Pepper Laboratory of the University Hospital. Cultures on Sabaroud's agar revealed three colonies of *Aspergillus fumigatus.* No fungi were found in a second specimen. This and the fact that this fungus is such a common air contaminant render the finding of *Aspergillus fumigatus* in one specimen of no significance, especially since there were no reasons whatsoever to suspect that this patient had pulmonary aspergillosis. The purulent material aspirated by puncture and irrigation of the left maxillary sinus by Dr. Houser was submitted to Dr. Forrester for examination for fungi and none were found.

In regard to the nature of taka-diastase, Mr. F. O. Taylor, the chief chemist of Parke, Davis & Co., informs me that it is produced from *Aspergillus oryzae* which has the property of producing a highly potent diastatic ferment during its growth. He states that the spores of the pure fungus, free from other types of fungi, are planted upon sterilized bran and grown under carefully controlled conditions of temperature and humidity. As soon as the pure fungus growth has developed to a sufficient extent to produce the maximum amount of diastatic activity, the diastase is extracted with broth, precipitated with alcohol, and purified by reprecipitation. It is then standardized by assay and adjusted to uniform standard of strength if necessary by the use of milk sugar as a diluent.

No other instances of sensitivity to taka-diastase have come to the attention of the manufacturer of this product.

SUMMARY

The case of a druggist is presented, who on two occasions developed violent attacks of asthma while compounding a prescription containing taka-diastase.

His clinical observation was substantiated by a strongly positive cutaneous reaction to this mold and by smaller positive reactions to other members of the *Aspergilli* and *Penicillia* species.

This case is presented merely as a matter of record in order to add taka-diastase to the long list of substances to which man may be allergic.

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Annual Review

IMMUNOLOGY

A Critical Review of Some Recent Developments in the Field of Allergy

Matthew Walzer, M.D., Brooklyn, N. Y.

AN ANNUAL review of the developments in the immunologic aspects of allergy would be, to a great extent, a repetition of the material which is presented in other departments of this Journal. I, therefore, consider it advisable to limit my discussion to selected subjects in the field. The choice of topics will be determined not solely by their importance, but, to a great degree, by their timeliness. Their presentation will be in the nature of a critical review for the purpose of clarifying, if possible, certain issues and of stimulating discussion on them.

TECHNICAL CONSIDERATIONS IN CUTANEOUS TESTING IN ATOPIC HYPERSENSITIVENESS

There have been few important practical suggestions in the last few years for improving the technic of skin testing. Rackemann and Simon[1] have recently emphasized the inadvisability of using asbestos-wound plungers in syringes employed for intracutaneous testing. They point out that this type of packing may absorb some of the allergen, which may not be destroyed by boiling, and thus confuse the results of subsequent testing with other allergens in this same syringe. The superiority of the all-glass syringe in this respect is stressed.

The importance of the choice of the cutaneous site for skin testing has again been emphasized in recent studies by Schmidt[2, 3] and Bowman.[4] Enlarging upon the earlier investigations of Alexander, Harter, and McConnell,[5] Schmidt reported that similar intracutaneous tests produced stronger reactions on the back than on the arms, on the forearm than on the arm, and on the flexor than the extensor surfaces. In testing on the back, he found that reactivity to similar tests with specific allergens and histamine was less above the level of the spine of the scapula than below it. In similar tests with histamine on the arm, Schmidt[2] found reactions near the elbow to be larger than those near the shoulder. He noticed no differences, however, in the reactivity of these areas to specific tests.

At about the same time Bowman[4, 6] was investigating the same problem from a different point of view. She sought to determine the degree

to which variability of cutaneous response in different areas on the arm would prevent or interfere with the ability to determine, by skin tests, the comparative strengths of two dilutions of the same excitant. She definitely demonstrated that, with the proper technic, one could differentiate, by comparative skin tests, between two dilutions of an allergen or of histamine, varying 25 per cent or more in concentration. A difference in 15 per cent, however, could not be detected. This corrected a common but erroneous belief that skin testing was a technic too crude to permit quantitative comparisons of extracts which differed but slightly in concentration.[7]

Bowman[4] reported the lower part of the arm in atopic patients to be more responsive to cutaneous tests with histamine than the upper part, a finding in agreement with that of Schmidt,[2] mentioned above. In testing with specific atopens, however, she found the reverse to be true, i.e., that the upper arm was more responsive to tests with allergens than the lower, a finding not noted by Schmidt. She pointed out that, in making comparative tests, the correct technic demanded that a series of trials be made, alternately reversing the relative positions on the arm of the extracts to be compared, in order that the location variable be eliminated. Other pertinent findings included the following: The identification of two solutions differing only 25 per cent in concentration succeeded when comparative skin tests were placed *vertically* on the arm *four* inches apart, but failed when that distance was only *two* inches. The most consistent results were obtained by placing the comparative tests in a *horizontal* plane, at least 1.5 inches apart. The latter finding is of significant practical importance in demonstrating that skin tests placed in a lateral relationship to each other, influence each other less than similar tests in a vertical plane. It suggests the advisability of inserting multiple skin tests for hypersensitiveness in horizontal rows on the arm rather than in vertical columns up and down the arm.

CUTANEOUS REACTIONS AND WHEAL FORMATION

The differences in the comparative responses of the upper and lower cutaneous areas of the arm to skin tests with atopens and histamine, as pointed out by Bowman,[4] gained additional significance in connection with another investigation by Bowman and Walzer.[8] In this study, other differences in the behavior of specific and histamine wheals were discovered. It was found that, when the site of a histamine wheal on an atopic patient was retested a week later with histamine, the resulting wheal was smaller than that on a normal control site, but that, when retested with a specific atopen, the resulting wheal was equal to the control. When the original wheal was specific in nature, however, restimulation of the site, one week later, with histamine or the specific excitant resulted in wheals larger than those on normal sites. It was apparent, therefore, that histamine and specific excitation were not

alike in their more lasting effects on the permeability of the vessels involved in wheal formation. Further clinical differences in the behavior of specific and nonspecific wheals had been previously brought out by McConnell[9] who reported that the cutaneous reaction to histamine was definitely increased during an allergic reaction, such as an attack of asthma, while the response to specific stimulation with allergens was not altered at this time. All these findings seem to point out new weaknesses in the theory that the allergic wheal is purely a histamine reaction. Although it may be true that the immunologic wheal is produced by some histamine-like substance, evidence is slowly accumulating which suggests that the specific (atopen-reagin) and nonspecific (histamine) reactions are far from identical, and that forces, other than the immediate ones, which produce the "triple response" (Lewis) are at play in these phenomena.

A new type of experimental immunologic wheal, which he has designated as the "reverse" type, has been described by A. Walzer.[10, 11] It was produced by passive local cutaneous sensitization with a reagin-bearing serum while the specifically related antigen was in the circulation and tissues. The "reverse" type of wheal was found to be smaller and less active than the "direct" type, in which sensitization preceded the antigenic stimulation. Its employment as a means of measuring the "tide" of unaltered protein in the circulation is discussed elsewhere. (See Absorption of Antigen.) Its distinctive feature was a deep seated nodular induration which persisted at the injected site for several or many hours. It gains significance in that it is the first type of experimental immunologic wheal which tends to persist instead of fading rapidly. This and its indurative property suggest a possible explanation of the mechanism of some of the more lasting types of wheals seen in some urticarias. While the size of the reverse wheal seemed always to be proportionate to the amount of antigen in the circulation, this relationship did not always apply in the case of the direct wheal. In the latter instance, A. Walzer[10] pointed out certain technical considerations which at times produced paradoxical results.

The influence which was exerted upon cutaneous reactions by medications which are commonly administered to control allergic symptoms, was studied by Tuft and Brodsky.[12] Adrenalin given subcutaneously tended to inhibit the formation of skin reactions. Ephedrine taken orally exercised much less influence than adrenalin on these reactions. Calcium gluconate and sodium iodide given intravenously did not affect them at all. Pituitrin and aminophylin did seem to influence the degree of cutaneous reaction to some extent but to a lesser degree than did adrenalin. The effects of all these medications disappeared within one hour.

The influence of exanthems on whealing response was studied by Pilcher.[13] In measles, scarlet fever, and in atropine flush, he found that

the whealing response of the skin to testing with codeine varied with the severity of the rash. The amount of fever exercised no influence on the whealing power. The results obtained seemed explicable on the basis of a nonspecific refractoriness to whealing produced at the site of the original rash. This refractoriness was temporary and was usually gone within a few days or a week.

Furstenberg and Gay,[14] in studying the effect of circulation on wheal formation, contributed an interesting observation. They found that passive local sensitization might be slightly more effective on a skin site to which the circulation was interrupted for a period of from ten to fifteen minutes than on a site to which there was a normal flow of blood.

Wheal formation, during the first two weeks of life, was studied by Carey and Gay.[15] They compared the cutaneous response of the skin to nonspecific stimulation (histamine) and specific excitation (Prausnitz-Küstner technic). They found that passive sensitization was regularly accepted even at this age but that there was considerable individual variation in the degree of wheal formation with both specific and nonspecific stimuli. They confirmed the findings of earlier workers (von Groer[17]) (Adelsberger[18]) that the skin, at this age, as compared to that of older subjects, showed a definite reluctance to whealing.

Curschmann,[16] reporting upon the influence of various physical agents and climate on wheal formation, found that, following sea bathing, the whealing response of the skin to morphine was unaffected but that the erythema was diminished. After exposure to the sun, the morphine wheal developed and disappeared more quickly than normally and, on the whole, presented less distinct stages in its development. This was accounted for by the hyperemic effect of the exposure to the sun.

EVALUATION OF THE RESULTS OF SKIN TESTING

The attitude of the allergist toward skin testing, as manifested in the recent literature on the subject, has undergone a decided change. Many writers are now taking a hypercritical and even derogatory stand regarding the value of the results obtained by skin testing. In some instances this represents a belated awakening to the limitations of the technic as a diagnostic procedure. For the most part, however, it is an attempt to arouse the practitioner to the weaknesses of the technic before it becomes totally discredited because of the exaggerated claims which have been made in its behalf. For this deleterious publicity, the overenthusiastic allergist is only partly to blame. He is being far outstripped in this respect by the proprietary advertiser who tries to coax the practitioner into believing that diagnosis in allergy depends merely upon the possession of a set of the proper allergens for skin testing.

The practical and theoretical considerations of the subject of skin testing were presented and analyzed at great length by Walzer and Thommen[19a] in 1931. The limitations of this procedure as a diagnostic technic were fully reviewed and emphasized. At that time, Alexander[20] and others were already engaged in attempting to educate the allergist as well as the practitioner concerning the pitfalls which awaited the inexperienced skin-tester. The recent publications on this subject seem to indicate that the allergist, at least, has begun to heed these warnings. But, in their anxiety to deflate and counteract the exaggerated claims and promises which have been made, most writers today are turning to the other extreme and are exaggerating the faults and deficiencies of the procedure. The subject of allergy has little to gain by excessive zeal in either direction.

The results to be obtained by skin testing naturally vary with each worker's technic, experience, and the type of patients which he studies. Hence, any single investigator's statistics on skin testing are of limited value. Only by striking an average of the results of many workers may some fair appreciation of actual facts be obtained. Realizing this, Alexander[20] in 1931 published such a statistical analysis. This should have served as a basis of comparison for subsequent statistical publications by individuals who investigated the incidence of reactions to particular excitants in various types of allergic patients and among normal persons. Unfortunately, these data were completely overlooked. Realizing its practical as well as theoretical importance, Alexander[21] again called attention to it in a recent publication. We consider these data sufficiently important to include some of them in this review. They should serve as a yardstick for comparison until larger and more detailed compilations are available. For these there is an urgent need. (Tables I and II.)

TABLE I

INCIDENCE OF REACTIONS WITH COMMON ALLERGENS (32,182 TESTS)

ALLERGEN	NO. TESTS DONE	% POSITIVE REACTIONS
Feathers { chicken, goose, duck }	5,491	20.3
Orris root	2,537	16.9
Horse dander	2,798	16.6
Wool	602	11.3
Pyrethrum	1,153	9.3
Cat dander	1,667	9.2
Cattle dander	745	8.7
Dog dander	365	8.3
All others less than 5%		

Writers[21, 22, 23] agree that the skin test attains its greatest accuracy and is of most value in the diagnosis of hay fever. It is less uniformly successful, although of unquestionable assistance, in the diagnosis of

hypersensitiveness in asthma,[21, 22, 19b] vasomotor rhinitis,[21, 22, 24] and atopic eczema.[21-27] It is less helpful in gastrointestinal allergy[21, 28] and only occasionally useful in urticaria.[20, 22]

TABLE II

ALLERGEN	NO. TESTS DONE	% POSITIVE REACTIONS
Wheat	1,999	22.4
Egg	923	18.4
Milk	1,176	14.8
Chocolate	285	13.9
Spinach	330	13.3
Bean	822	12.9
Potato	604	12.1
Tomato	522	11.9
Carrot	329	11.8
Pea	548	11.5
Barley	644	10.7
Rye	946	8.9
Pork	508	8.3
Beef	527	7.7
Oat	1,711	6.7
Corn	1,774	5.7
Rice	635	5.7
Pepper	452	17.5
All others less than 5%		

The limitations of the skin test as a means of arriving at a diagnosis have been thoroughly discussed by the above writers[19-28] and many others. The warning is repeatedly sounded against any rigid or arbitrary method of interpreting skin reactions. It has become apparent to all that, in most allergies, a creditable percentage of diagnoses will not be arrived at by following any set of rules as to method of preparation or choice of allergen, performance of test, or reading of results. With this technic, as in the case of every other complicated diagnostic procedure, there is no substitute for experience and perserverance in learning to apply it effectively.

Realizing the limitations of many reports of clinical studies which are stated in terms of percentages of positive reactions obtained, Colmes[22] offered the suggestion that it would perhaps be more profitable to write in terms of percentages of reactions which are proved to be clinically significant. This would be a step in the right direction; although it is not entirely practicable and also has its limitations. It would seem to this reviewer, however, that no standard method of reporting results could possibly be satisfactory for all purposes. The most urgent need, at present, is a more complete description, in the publications on skin testing, of the exact technic and of the nature of the materials which have been employed, as well as of the standards by which the results of testing have been read and interpreted. With such complete records and protocols available, each reader would be in a position to interpret the experimental data himself and to draw his own conclusions.

The difficulties to be encountered in the proper evaluation of the results of skin testing are well illustrated in the published reports of the incidence of positive reactions obtained in studies of "normal" groups of subjects. Rackemann and Simon,[1] testing 60 supposedly nonallergic individuals on the hospital wards with 8 allergens, found positive reactions in 50 per cent of them. Twenty per cent of the patients reacted to ragweed and 36.3 per cent to silk floss. These two figures alone are in such disproportion to the usual reported incidence of such reactions, even among allergic cases, as to cast considerable doubt upon the specificity of many of the reactions which were obtained. It seems probable that some technical factors, in the performance of the tests, in the nature of the allergens, or in the interpretation of results, were responsible for eliciting such a high percentage of supposedly positive reactions in this study. Moreover, many of the subjects eventually admitted positive personal or familial atopic histories, thus further discrediting the value of the statistics from the point of view of an analysis of normal (nonatopic) subjects.

Grow and Herman[30] also published results of a study of skin testing on 150 supposedly normal individuals. They reported an incidence of 55.5 per cent of positive reactions in this series. Interpretation of these figures is also subject to many reservations. Forty of the subjects gave suspicious personal or family histories of allergy. Intracutaneous tests were performed with 0.05 c.c. of extract. Even "faint" reactions were included among the positives. Under the circumstances it is not surprising that unusual results were obtained, such as, 38.6 per cent of the group reacting to horse dander (0.1 mg. N per c.c.), 34.6 per cent to orris root (0.035 mg. N per c.c.) and 32.6 per cent to lobster (0.05 mg. N per c.c.). (See Tables I and II for usual averages.)

Harkavy and Romanoff[31] tested 200 unselected subjects with 5 tobacco extracts (0.06 to 0.09 mg. N per c.c.) and with ragweed pollen, timothy pollen and horse dander extracts (0.01 mg. N per c.c.). Forty-two per cent reacted to one or more of these tests; 38 per cent to one or more tobaccos, 24 per cent to ragweed, and 13 per cent to timothy. In this series also, the plus-minus reactions were included among the positives. With the dilutions and allergens employed the number of nonspecific reactions was undoubtedly large. (See Tobacco Hypersensitiveness.) As the purpose of the study required that atopics should not be excluded from the group, the value of the results obtained are limited in statistical analyses of reactions in nonatopic individuals.

No studies on atopic reagins in association with the supposedly positive skin reactions were included in any of the above communications.

The above publications have received special attention because they are quoted—and some of the above authors make the implication—as evidence that at least one-half of the population is allergic. For reasons

already stated, I do not believe that the data which were presented justify such a conclusion. Moreover, my own skin testing in normal persons has yielded results not in agreement with those quoted above.

Since 1926 I have been using supposedly normal individuals as substitutes for the indirect testing of certain atopic patients. In this procedure, not only the sites sensitized with the patient's serum are tested with the various allergens, but corresponding control tests with the same amount of the material are injected into the normal unsensitized skin. Information is thus available on a large series of supposedly normal individuals who have been completely tested with routine foods and inhalants. A complete analysis of these data will eventually be published. For the present, however, the following information will be presented as pertinent to this discussion.

The substitutes were of two types. Many of them were hired and had been selected from many applicants because they presented absolutely negative personal and family histories of allergy and because they possessed skins which were not irritable. The others were relatives or parents of the patient who volunteered their services and who denied any knowledge of allergy in themselves or in "their side of the family."

These two groups responded quantitatively differently to testing. The normal (nonrelated) group, when tested with relatively nonirritating allergens (such as horse, cat, and dog danders, cottonseed, orris, etc.) in ordinarily nonirritating dilutions (0.01 mg. N per c.c. or less), showed only an occasional borderline reaction and very rarely a definite positive reaction (more than one-plus). The "normal" relatives, when tested with these same substances, showed more than twice as many reactions as the nonrelated group, and, of these, a large proportion were definitely positive. Yet the positives on these "normal" relatives did not begin to approach in number or degree those which were manifested by the atopic patient for whom they were acting as substitutes.

In contrast to these results were those obtained by testing with irritating extracts, such as house dust, feathers, goat hair, wool, etc. The related and nonrelated groups reacted almost alike, both in the frequency and in the degree of positive reactions to testing with these substances, thus definitely establishing the nonspecific nature of the stimulation. Almost every substitute reacted to one or several of these irritating allergens to a degree varying from a borderline to a marked reaction. The distinction between the substitutes and atopic patients was much less clear on the basis of reactions to this group of allergens than it was with the nonirritating substances.

Hence, it may be concluded that almost anyone may show a positive reaction when tested with an irritating substance. Such reactions cannot be held to be evidence of atopic hypersensitiveness unless they can be transferred by the Prausnitz-Küstner technic to a skin which itself does not manifest the same sensitivity. Positive reactions on normal

or atopic persons, if not submitted to corroboration by passive transfer, can merit serious consideration only when they are elicited by allergens which are nonirritating. This quality of the test substance cannot be judged by its dilution or by its nitrogen content, but by actual trial with it on a large series of cases.

In view of these facts there is a certain amount of information to which the impartial reader is entitled in future publications in allergy on the incidence of positive skin reactions. He should be informed of the percentage of positive reactions which are obtained with *nonirritating* test materials. If the extracts are irritating, he should be enlightened as to the percentage of these positive reactions which can be transferred by the Prausnitz-Küstner technic. And finally, in connection with positive reactions, he has a right to know whether borderline or doubtful reactions are included in the figures and what percentage of the total they represent. When statistical material of this nature is presented, the conclusions will be obvious and irrefutable.

ACTIVE SENSITIZATION IN HUMAN BEINGS

All attempts to reproduce the atopic type of hypersensitiveness in human beings have thus far met with little success. Attempts at sensitization by Brunner[32] with rabbit epithelium, egg white, and cat epithelium, given by weekly subcutaneous injection, in a series of 15 atopic individuals, over a period of from 9 to 32 weeks, were almost uniformly unsuccessful. Only one individual, naturally sensitive to ragweed and rabbit epithelium, developed a positive reaction to orris root after 17 injections, but this technic failed to induce hypersensitiveness with the same antigen in 7 others. The sensitivity to orris in this one instance was transient, disappearing within a few months after the injections were stopped. Hence, with this one exception, Brunner was unsuccessful in stimulating, in atopic individuals, the protracted formation of reagins to some of the commonest atopens in clinical allergy. Simon and Rackemann,[33] likewise reported their failure to sensitize any human beings by repeated intracutaneous injections of egg white and cow's milk. Hoping for better success with antigens with which the subjects were not in constant contact, they employed turtle eggs and mare's milk in large doses but with negative results.

Only with ascaris antigen could the formation of atopic reagins be stimulated by Brunner[32] with any degree of regularity. Here again, their production was short lived and disappeared within a few months or a year. Brunner and Baron[34] found the production of ascaris reagins to be as easily induced among nonatopic as among atopic individuals. The ease with which reagins can be produced with ascaris antigen in almost all individuals probably rests in some peculiar quality of the antigen and not on the susceptibility of the subjects.

Reagins may frequently be produced by the injection of horse serum,[35] rabbit serum[36] and guinea pig serum.[37, 38] They are occasionally formed in certain types of insulin hypersensitiveness.[39, 111] These artificially induced reagins are produced under circumstances which are quite different from those surrounding the appearance of reagins in the ordinary atopic illnesses. In the latter instances, Coca[40] points out, contact with the excitant is almost always by natural channels; the reagins result from stimulation with "poor" antigens, such as pollen; and finally the reagin production is subject to the atopic hereditary influence from the point of view of age of onset in their production.

In contrast to the difficulty encountered in the production of the atopic type of hypersensitiveness to clinically common atopens is the ease with which a *non-hereditary* type of hypersensitiveness may be produced to animal serums and certain other animal proteins. Several workers, continuing in a field of investigation already travelled by Hamburger and Pollak[41] and others, have enlarged our store of knowledge of this frequenty encountered but clinically less significant type of hypersensitiveness. Jones and Mote[36, 42, 43] studied the various stages in the development of this type of sensitivity. Working first with streptococcal material in rabbit peritoneal fluid, but later with rabbit serum alone, they noted that repeated intracutaneous injections were likely to produce, at first, a delayed type of reaction five to fourteen days later. This was probably a manifestation of local serum disease. After further treatment came a delayed reaction about twenty-four hours after the injection. With continued stimulation, a certain percentage of these cases developed an immediate cutaneous reaction to the injection of the rabbit serum, followed at times by the delayed type but later without it. The regression of the sensitivity occurred in the reverse order of its appearance; i.e., the twenty-four-hour delayed reaction usually outlasted the immediate one. Sensitivity was produced in 82.6 per cent of human beings treated with rabbit protein. There were wide variations in the type of sensitivity, the rapidity of its development, and the duration of the various stages, etc. This hypersensitiveness did not tend to become permanent, although it persisted in some cases for more than two years.

No antibodies were found to accompany the delayed reactions. With the immediate type, however, precipitins and occasionally reagins to rabbit serum were found. The plain rabbit serum was not so actively antigenic as the streptococcal rabbit serum preparation in the production of cutaneous hypersensitization. This was to be expected in the light of the earlier findings of Tuft and Ramsdell[44] and Coca[19c] that little or no antibody formation followed injections of normal horse serum into human beings but much more was encountered with the use of immune serums.

Tezner[45, 46] investigated the subject of induced immediate and delayed reactions, but limited his period of observation to four weeks. Like the

other workers, he found that, following daily intracutaneous injections of 0.1 c.c. of horse serum, a delayed reaction preceded the immediate one in the development of cutaneous hypersensitiveness. It usually appeared at the end of the first week or at the beginning of the second. The Prausnitz-Küstner reaction became positive shortly after the delayed reaction developed and usually persisted after the latter had disappeared. Working with egg white, he succeeded in reproducing virtually all the phenomena observed with horse serum, but failed completely when using house dust as an antigen. He believed that the immediate and delayed reactions were mediated by two closely related and mutually interchangeable antibodies and that clinical sensitivity differed from the induced type only quantitatively.

Almost coincidentally with the first publication of Jones and Mote appeared the results of sensitization experiments by Rackemann and Simon[38] performed with intracutaneous injections of guinea pig serum. For the most part they agreed with the findings of Jones and Mote. They made the important additional observation that these sensitivities were produced as easily in nonatopic as in atopic individuals. In a subsequent study these authors[37] attempted sensitization by means of repeated intranasal instillation of guinea pig serums. They succeeded definitely in 4 out of 9 cases and obtained doubtful results in two others. When cutaneous sensitization developed, a subsequent instillation of the antigen resulted in nasal symptoms simulating hay fever. The writers stated that, in the presence of the delayed type of cutaneous sensitivity, the nasal symptoms were delayed for six to twenty-four hours, whereas with the immediate type they started almost at once. In three cases no nasal symptoms were obtained, even though immediate or delayed skin reactions were present. This failure to develop nasal mucous membrane sensitivity in about one-half of the cases corresponds roughly with the findings of Tuft[35] in the ophthalmic sensitivity of children who had been immunized against diphtheria with toxin-antitoxin. In his series 28 per cent were found to have positive skin tests to horse serum after this treatment, but only 15 per cent had positive ophthalmic reactions.

In connection with the nasal sensitization experiments of Rackemann and Simon, it is important to note that the nine subjects used were all atopic and were subject to ragweed hay fever, vasomotor rhinitis, or asthma. The atopic shock organ, present in all, was therefore subjected to stimulation by a type of acquired hypersensitiveness in which, as was shown above, atopic reagins were frequently present for short periods of time. These antibodies, however, are not absolute prerequisites for stimulation of the atopic shock organs. This was demonstrated by Coca[19d] in the case of Dr. T., an atopic individual who manifested immediate severe symptoms following an injection of horse serum, although no reagins for this atopen were present in the blood. Ragweed reagins were present, however, and the patient manifested a positive

ophthalmic reaction to horse serum. The sensitivity to horse serum in this case, therefore, was probably of the acquired type but of unusual intensity.

In spite of his success in the above experiments, Rackemann[47] has expressed justifiable reluctance in believing that this artificially induced type of sensitivity is the same as the natural atopic form. He commented on the fact that, in its transitory nature and in its mild form which cannot be intensified at will, it does not resemble the clinical sensitivity of atopy. This raised in his mind the "grave question whether the behavior of an allergic person does not depend on something more fundamental than a mere quantitative change in sensitivity. The whole question of the influence of heredity in allergy is still pertinent." In the light of the experiences of Park[48] and others that the acquired cutaneous reaction to horse serum is of little clinical significance and is no contraindication to serum administration, it seems obvious that this easily acquired type of horse serum sensitivity, which is as readily induced in normal as in atopic persons, gives information which is limited in its application to the more serious problem of atopic hypersensitiveness.

In connection with the easily induced types of hypersensitiveness in human beings, it will be noted that the only substance which was almost uniformly successful in producing it was the ascaris antigen. A fair degree of success was obtained in the above studies with animal serums (rabbit, guinea pig, horse, etc.). Failures were recorded with cat epithelium, cow's milk, egg white, house dust, mare's milk, rabbit epithelium and orris root (with one questionable exception). Brunner[32] and Rackemann and Simon[33] failed to induce it with egg white in adults, but Tezner[45] succeeded in children.

When sensitivity was successfully induced, the technic employed seemed of secondary importance. Weekly or daily injections, intracutaneously or subcutaneously, seemed to accomplish the same result, although there were quantitative variations. *The nature of the antigen,* however, seemed to be the primary factor responsible for the success obtained in inducing this form of cutaneous sensitization.

Opposed to this concept is another which maintains that the degree of exposure is the primary consideration in inducing this type of hypersensitiveness. Evidence in its favor may be found in recent studies[49-51, 110] on workers in various industries which purport to show that individuals, as a group, manifest more positive reactions to the occupational allergens to which they are exposed than to those encountered in other trades. Of these investigations, two were made on series of atopic patients and two on unselected groups of trade workers.

Moll[51] reported a higher than usual incidence of wool reactions among his allergic patients who were engaged in the wool industries. Positive reactions to animal danders in his series of 119 sensitive cases occurred as follows: feathers, 36.1 per cent; sheep's wool, 18.4 per cent; cat

epithelium, 9.2 per cent; dog epithelium, 8.3 per cent; rabbit epithelium, 5.8 per cent cattle epithelium, 0.8 per cent; and horse epithelium, 0.8 per cent. A comparison of these figures with the common averages listed by Alexander[20] (see Table I) leaves little to support Moll's claim that occupation alone is responsible for the high percentage of wool reactions among his patients. The wool reactions obtained by him do not seem out of proportion to the feather, cat, and dog reactions, all of which are slightly higher than the average. His failure to find a higher percentage of horse epithelium reactions in such a large series of cases is unexplainable.

Baagöe[110] tested 17 bakers, suffering with vasomotor rhinitis and asthma, and found that 76.4 per cent of them gave positive reactions to cereals, 6 per cent to animal danders (including feathers), and 6 per cent to pollens. In comparison with these figures were those obtained in 47 hay fever patients among whom cereal reactions totalled 0 per cent, animal danders 21 per cent, and pollens 100 per cent. Tests on 300 asthmatic persons gave an incidence of 21 per cent positive reactions to cereals, 48 per cent to animal danders, and 15 per cent to pollens. The Prausnitz-Küstner phenomenon was demonstrated in 4 out of 5 patients with positive cereal reactions. Insufficient details were furnished as to the technic employed in this investigation. Moreover, this series is not large enough to justify the drawing of any conclusions from it.

In the first of the studies on unselected cases, Colmes, Guild and Rackemann[50] tested a group of 32 workers in a bakery. Of these, only 3 were frankly atopic. They found 15 (47 per cent) sensitive to one or more cereals. No tests were made on normal controls. Control tests on 19 allergic patients who were not clinically sensitive to cereals revealed positive reactions to these allergens in 13 (68 per cent) of them. This unusually high figure raises a doubt as to the specificity of some of the positive reactions obtained in the 32 bakery workers with these cereal preparations.

An extensive investigation on the subject was made by Salen and Juhlin-Dannfelt.[49] Testing workers in various industries with wheat, they found positive reactions among them as follows: bakers, 20 per cent; theater personnel, 0 per cent; warehouse workers, 2 per cent; and veterinarians, 0 per cent. With rye, the positive results were: bakers, 37 per cent; mounted guards, 4 per cent; and garment workers, 5 per cent. Tests with horse dander in the various industries revealed positive reactions as follows: mounted guards, 23 per cent; bakers, 8 per cent; and veterinarians, 9 per cent. Among the latter, an unusual observation was made in that all the positives (6) occurred among 40 veterinary students and none among 29 practicing veterinarians. Many of the subjects in the various groups studied were allergic, but the incidence of the positive reactions seemed to bear no relationship to this factor. Passive transfer studies were more frequently successful with the cereal reactions

than with the horse dander ones. The statistical value of the results obtained in this work is unfortunately limited for comparative study because of the technic employed. For intracutaneous testing, 0.1 c.c. of extract was used, and the reading of reactions was necessarily made on standards different from those employed by most other workers.

In both the studies[49, 50] on groups consisting for the most part of nonatopic individuals, it was reported *that the positive reactions obtained were not an index of clinical sensitivity.* They were found among nonatopic as well as among atopic persons. In this respect the reported reactions resembled the easily acquired type described above.

Before making further comparisons or entering into deeper discussions as to the nature of the reactions, it seems advisable to await more information concerning them. More occupations should be studied, and the data already available should be checked.

From the point of view of atopic hypersensitiveness, however, the above results will not necessarily be applicable. It seems obvious that neither the quality of any antigen nor the degree of exposure to it is in itself sufficient to account for the sensitivities which are clinically manifested in hay fever, asthma, and other atopic illnesses. In seeking for the final determinant of the time of onset, form, and degree of clinical atopic hypersensitiveness, there is no more adequate concept than that of Coca, who maintains that hereditary tendencies influence the choice, time of onset, and behavior of the "shock" tissue, as well as the nature of the sensitivity. There are, however, many secondary factors participating in the etiology and symptomatology of atopic illnesses which need further clarification.

AGRANULOCYTOSIS

Most writers credit Pepper[52] (1931) with originating the theory that agranulocytosis following drug administration is an allergic manifestation. More and more this idea has gained in popularity so that today it is given serious consideration by most workers in the field and accepted by many. The condition is vaguely referred to as a "hypersensitivity," "idiosyncrasy," "susceptibility," or "allergy."

Considering the popularity of the theory, it is indeed surprising that there has been almost no experimental evidence to substantiate it. Whatever work has been done has served to weaken rather than strengthen the hypothesis of an immunologic mechanism in agranulocytosis. The theory seems to have won favor, not because of its own merit, but because of the inadequacy of other concepts. The statement is encountered repeatedly that the illness "must be a hypersensitiveness," because, since only a few individuals are affected, it cannot be a toxicity.

The drugs which are definitely incriminated[53] as the causes of agranulocytosis are amidopyrine and dinitrophenol. The evidence against or-

ganic arsenical compounds and gold salts is also very strong. Barbiturates and other coal tar derivatives are suspected, but the case against these has by no means been proved.

Attempts to reproduce the disease in animals have met with only limited success. Little as it is, however, it is sufficient to cast considerable doubt upon the allergic theories. Madison and Squier[54] induced a typical agranulocytosis in one of eleven rabbits which had been receiving daily doses of from 2 to 24 grains of allonal (allylisopropylbarbituric acid with amidopyrine). The affected animal, which had been receiving about 20 grains daily, manifested a marked drop in the total white cell and granulocytic count on the twenty-fifth day. These figures fell progressively until death occurred on the thirtieth day, at which time granulocytes were entirely absent in the blood and in the bone marrow. The other rabbits receiving oral medication, as well as eight others receiving intraperitoneal and intravenous doses, showed negative findings.

Kracke[55] and Parker[56] have been able to induce various degrees of neutropenia in animals by intravenous or subcutaneous injections of benzine or some of its oxidation products, especially catechol and quinone. They pointed out that all the drugs definitely associated with granulocytopenia contain a benzine ring with an attached amine group, and that catechol and the quinones are the oxidation products of these substances. They[53] correlated these findings with the fact that benzine is the only drug which has experimentally produced profound leucopenias with any degree of consistency. Moreover, Kracke[55] noted that, if sufficiently small doses of benzine were given to rabbits, only the myelocytic tissues were affected and a typical clinical agranulocytosis could be induced. Larger doses affected the erythroblastic tissues as well. Hoffman, Butt, and Hickey[57] were also able to induce a depression of the total white count in rabbits by the oral administration of amidopyrine for a period of several weeks. Climenko[58] found that he could counteract the leucocytic stimulation of nucleic acid in rabbits with catechol, quinone, dinitrophenol, and other benzine derivatives. Dameshek[59] stated that he was able to induce leucopenias in normal individuals by the continuous administration of amidopyrine.

Such experimental evidence still leaves much to be explained in a toxic theory of agranulocytosis. Most advocates of the theory are therefore willing to concede that, in addition to the toxic element, there is some "predisposition" on the part of the patient to account for the rarity of the condition. This does not necessarily predicate an immunologic "predisposition"; in fact, the evidence thus far tends to exclude this possibility.

Hunter[60] analyzed all the published histories of agranulocytosis to determine the frequency of recognized types of allergy among these individuals. His study included 177 cases caused by drugs and 7 caused by various foreign proteins which had been described by other writers, as

well as 27 of his own cases. He concluded that "there is not enough evidence in the literature or in the author's series of cases to state that injury to the blood-forming organs from the use of drugs or foreign protein occurs more frequently in frankly allergic individuals than in normals."

There is not sufficient evidence of cutaneous hypersensitiveness which might be cited to strengthen an immunologic theory in granulocytopenia. Benjamin and Biedermann[61] failed to obtain positive reactions with cutaneous testing in their cases. Limarzi and Murphy[62] were no more successful with patch testing in their series. Dameshek and Colmes[59] obtained negative results with patch and scratch testing in their four cases. They reported that they obtained immediate positive reactions by testing with a mixture of blood and drug, which had been allowed to stand for several days. Positive reactions, however, were also found among normal controls. Squier and Madison[63] alone reported positive results in two of their three cases as a result of patch tests with the drug. As noted above, other workers have failed with the same technic. There is little, then, to fortify an immunologic theory in the above findings.

Coca[64, 19c] has called attention to the fact that "a drug does not produce its peculiar effect upon the hypersensitive person through the usual medium of its toxic action, but through a different mechanism, which is the same in all drug allergies." The allergic theory of agranulocytosis loses ground on this count as the "immunologic" reaction to amidopyrine is similar to, if not identical with, the toxic action of the drug. Furthermore the "mechanism" involved is not one which is common in drug allergy but one which seems to be characteristic of preparations containing benzine and certain derivatives of it.

What then are the arguments advanced in favor of the allergic theory? Considering the popularity of the concept, the paucity of literature dealing with the theoretical aspects of the subject from the point of view of hypersensitiveness is surprising. Of the available articles,[59, 60, 61, 63, 65] Hunter's[60] is the most complete and includes practically all the arguments in favor of an allergic theory. Of these, the strongest may be presented briefly as follows: (1) Agranulocytosis has not been reproduced with infectious agents. (2) Since only certain predisposed individuals are affected, the condition is not a true drug poisoning. (3) The violent onset of the illness with chills and fever simulates the reaction following injections of foreign protein. (4) Neutropenia, similar to agranulocytosis, is found in acute allergic shock and serum disease. (5) The syndrome does not develop upon first contact with the drug. (6) A minute dose can cause a recurrence of symptoms.

Hunter considers the resemblance between agranulocytosis and the neutropenia found in acute allergic shock and serum disease an argument "of great significance." Vaughan,[66] however, points out that in the neutropenia, following the ingestion of foods causing allergic symp-

toms, the reaction is not limited to granulocytes but involves all types of white blood cells. Rackemann[47] attaches the greatest importance to Hunter's argument that the illness never occurs on the first exposure, but always at some subsequent administration of the drug. If this could be proved, he believes that it might, indeed, be significant. Difficulties, however, prevent the establishment of such proof, because the primary effects of the drug are not always detectable by blood studies. Miller[67] fed amidopyrine to dogs without influencing the granulocytes in the circulation, but bone marrow studies revealed definite damage to some of the blood-forming cells. Under these circumstances one usually is not in a position to judge how long the drug has been at work before clinical and hematologic symptoms of agranulocytosis develop.

The evidence favoring an immunologic theory seems, therefore, to be inadequate for its proof. Although there are many weaknesses in the toxic theory, it seems at present to be the more acceptable of the two, as it is in closer accord with the known facts.

IMMUNOLOGIC METHODS OF DIAGNOSIS IN TRICHINIASIS

Considerable interest has recently been aroused in immunologic aids in the diagnosis of *Trichinella spiralis* infections. This work, which was started by Bachman[68, 69] in 1928, has recently been brought to the fore again by the publications of Augustine, Theiler, and their associates.[70-73] Bachman, working on experimentally infected animals, demonstrated the diagnostic value of precipitin and skin tests in *Trichinella spiralis* infections. The skin reaction which he described was a delayed one. Augustine and Theiler applied their tests to human beings. They made their diagnosis on the basis of an immediate cutaneous reaction.

Using an intracutaneous test of 0.1 c.c. of a 1:10,000 dilution of trichinella antigen, Spink and Augustine[71] obtained immediate positive reactions in 33 out of 34 cases of trichiniasis. The reaction could usually be obtained after the seventeenth day of the illness. In some cases they observed it as early as the fourth week of the illness, a fact which tended to detract somewhat from its value as a diagnostic aid. From the point of view of early onset, the eosinophile count seemed to be of the greatest assistance, usually appearing in the second week and reaching its height during the third.

McCoy, Miller, and Friedlander[74] also found the intracutaneous test very helpful in the diagnosis of trichiniasis. When negative reactions were obtained with a 1:10,000 dilution of the antigen, they repeated the test with a 1:500 dilution. They reported positive reactions as early as the eleventh day of the illness. They found that more than 90 per cent of their infected cases reacted to skin tests with the trichinella antigen, but a certain small percentage of frank trichiniasis cases never became sensitized.

Although the degree of sensitivity slowly diminishes with time, positive skin reactions have been demonstrated from four to nine years after the infection.[72] Weakly positive precipitin tests and slight degrees of eosinophilia were also found to persist at this time.

Skin tests by McCoy and his associates[74] on supposedly normal controls revealed a certain percentage of positive reactions which varied with the locality. In Rochester, New York, about 7 per cent of subjects reacted to a 1:10,000 dilution of the antigen and about 18 per cent to a 1:500 dilution. The incidence of positive reactions among the atopic members of this group, when tested with a 1:10,000 dilution, was 11 per cent. In San Francisco, only about one-third as many positive reactions were obtained on normal controls as in Rochester. The group tested, however, was much smaller and the average age much younger. Tests were also carried out on a group of Louisiana subjects, most of whom were known to be infected with *Trichiuris, Ascaris,* or other types of parasites, but who resided in a district where trichiniasis was considered a rarity. Eighteen per cent of this group reacted to the 1:10,000 dilution of trichinella antigen and 62 per cent to the 1:500 dilution. The authors were, therefore, convinced that group reactions were being obtained with the stronger trichinella extract (1:500) which could be diminished but not totally eliminated by testing with a higher dilution (1:10,000). Realizing these limitations of the technic, McCoy and his associates were more conservative than Theiler and Augustine in the evaluation of the skin test as a diagnostic procedure in trichiniasis. They concluded that a "negative test will probably prove more useful in ruling out the diagnosis of trichiniasis than a positive one in establishing it."

Study of the precipitin tests in trichiniasis has revealed a high degree of specificity in the procedure and has established its worth as an aid in the diagnosis of the illness.[73] The reaction was positive in about 90 per cent of infected animals in the series of Bachman[75] and of Maternowska.[76] These workers reported that group reactions as a result of associated infections with *Trichiuris, Ascaris,* or *Echinococcus* did not commonly interfere with the specificity of the precipitin test to the trichinella antigen.

When negative results are obtained with the intracutaneous test with trichinella antigen on suspected cases of trichiniasis, the procedure is naturally repeated at various stages of the illness to detect, if possible, a later onset of sensitivity. Goldschlager[77] suggested that the diagnostic value of tests diminished after the first one, as sensitization might be induced by the intracutaneous test itself. Most workers, although cognizant of this possibility, ignored it as a practical consideration. Recent experiments by Baron and Brunner,[78] however, seem to indicate that this error in technic is probably responsible for some of the unexplained positive reactions which are being reported. These workers had no diffi-

culty in sensitizing normal subjects by repeated intracutaneous tests with trichinella antigen. Sensitivity in some cases was induced by the first test. As in the case of the ascaris antigen,[32] atopic reagins were proved to be responsible for the immediate positive cutaneous reactions. By passive transfer experiments, they found that there is an antigen common to the *Trichinella* and *Ascaris* worms. Under the circumstances the reported failure of these antigens to produce precipitin reactions in common needs further investigation.

TOBACCO HYPERSENSITIVENESS

In October, 1932, Harkavy[79] and his coworkers published the first of a series of communications in which the concept was introduced that thromboangiitis obliterans is an allergic disease and that tobacco hypersensitivity is its most frequent cause.[31, 79-83] Almost coincidentally Sulzberger[84-87] started a series of his own, entertaining the same theory. These hypotheses were developed in the next two years and were elaborated by Harkavy to include, under the category of allergic conditions, such illnesses as coronary disease, migrating phlebitis, and gastroduodenal ulcer.

Because this work has attracted so much attention and because the principles involved are so revolutionary in the field of immunology, the subject deserves careful consideration. The important findings will therefore be briefly summarized (without regard to their chronologic order), and an analysis of the data will be attempted.

In most of his studies, Harkavy used individual extracts of the uncured leaf of Burley, Maryland, Virginia, and Xanthis (Turkish) tobaccos for testing. As an additional test, he also employed "Coca's extract" which represented a denicotinized extract of a mixture of several tobaccos. The various extracts were prepared according to Coca's technic. Each subject was tested intracutaneously with 0.01 to 0.02 c.c. of each of the 5 tobacco extracts in a dilution of 1:10. This dilution was necessary in each case, "because the original solution was irritating and produced false positives."[79] In addition, tests with ragweed and timothy pollen and with horse dander were also made with extracts in a dilution of 0.01 mg. N per c.c. Tests were read in about fifteen or twenty minutes after testing. "A plus-minus reaction was one in which the erythema was negligible but the wheal distinctly larger (about 5 mm.), as compared with a completely negative reaction to diluent or other control allergens. A one-plus reaction consisted of a wheal approximately 5 mm. in diameter and an erythema between 1 cm. and 2 cm."[31]

In the statistics the plus-minus reactions were included with the positives. An individual was counted among the positive reactors to tobacco if he manifested as much as a plus-minus reaction to *any one* of the 5 different tobaccos tested.

Harkavy[82] reported that positive reactions to tobacco were found in 86 per cent of his cases of thromboangiitis obliterans. As controls, he tested 319 male smokers, most of whom were hospital patients, and found 20.4 per cent positive to tobacco. Among 126 female nonsmokers, most of whom were hospital patients, 12 per cent reacted to tobacco. Among these controls there were no atopic subjects. In another study[31] on 200 controls, consisting of smokers, male and female, and including atopic subjects, 38 per cent reacted to tobacco. These were equally divided among the two sexes. Retesting of 69 thromboangiitis obliterans cases at this time revealed an incidence of 78 per cent positives to tobacco.

Among other illnesses, Harkavy[82] found tobacco reactions in 43 per cent of 71 male smokers with coronary artery disease, in 26 per cent of 60 cases with gastric or duodenal ulcers, and in 40 per cent of five cases of migrating phlebitis.

The serums of 22 thromboangiitis obliterans patients who reacted to tobacco were tested for atopic reagins by the Prausnitz-Küstner technic. Positive results were obtained in 15 of them.[80] Four out of ten patients who reacted to tobacco also reacted to tobacco smoke. Skin tests with nicotine tartrate were uniformly negative in all of the cases of thromboangiitis obliterans.

Sulzberger[85] reported his results on a series of 22 thromboangiitis obliterans patients. These were tested by the intracutaneous method with 0.01 c.c. of various extracts of individual tobaccos, or with a mixture of several tobaccos. The extracts were used in various strengths, but most of the tests were made with an undiluted extract of a mixture of several tobaccos.

Among Sulzberger's 22 cases, 17 gave positive reactions to tobacco. Among controls consisting of 95 smokers, male and female, chosen from a hospital population, 36 per cent gave positive reactions to tobacco.[86] The same percentage was found among 38 healthy smokers who were similarly tested. Among 58 nonsmokers in a hospital population, 16 per cent were positive to tobacco. Among 73 cases of heart disease (hypertensive and arteriosclerotic, and rheumatic), only 22 per cent showed positive reactions to tobacco. Skin tests with nicotine sulphate solution (0.4 per cent) were negative or almost negative in all cases of thromboangiitis obliterans.[84, 86] The tobacco excitant was found to be thermo- and coctostabile. Some patients were found sensitive to a single brand of tobacco and negative to all others. In some cases delayed reactions to tobacco occurred after twenty-four or forty-eight hours.

Sulzberger[85] found reagins to tobacco in only one of his 22 cases. Atopic, personal, or family histories were no more frequent among these thromboangiitis obliterans cases than among a control group of normals.

Both Harkavy[79] and Sulzberger[87] found positive reactions among their thromboangiitis obliterans cases to other allergens in addition to tobacco,

and suggested the possibility that such sensitivities might also be the cause of the disease. They considered tobacco, however, as the most important offender.

We thus find Harkavy and Sulzberger confirming each other on some findings and contradicting each other on others. They both reported that tobacco reactions were more frequent in thromboangiitis obliterans cases than in other control groups. In this, they were not confirmed by Trasoff and his coworkers[88] who tested various groups of cases with some tobacco extracts used by Harkavy and Sulzberger as well as with some of their own. The intracutaneous technic was employed using 0.01 to 0.02 c.c. of extract for each test. Among 31 cases of thromboangiitis obliterans, they found 16 per cent reacting positively to tobacco. Among 23 patients with coronary disease, 13 per cent were positive. Testing healthy individuals revealed an incidence of 21 per cent in 52 nonsmokers and 17 per cent in 40 smokers. Among allergic subjects 47 per cent of 17 smokers and 25 per cent of 24 nonsmokers showed positive reactions. The only definite increase in tobacco reactions therefore appeared to be in the allergic groups.

A comparative analysis of results of these different workers is impossible because of the lack of sufficient protocols in their publications. Harkavy presented detailed protocols of the skin tests of his controls but none of his thromboangiitis obliterans cases. Sulzberger furnished no detailed information on his controls. Trasoff gave only a summary of his findings.

It is not easy to understand the wide divergence of results in the matter of reagins. Harkavy[80] claimed to have succeeded in demonstrating tobacco reagins in 15 of 22 thromboangiitis obliterans cases with positive reactions to this allergen. Sulzberger,[85] however, found them in only one of his 22 cases. Trasoff[88] reported only one successful transfer in many attempts. One may not venture to interpret the theoretical significance of the tobacco reactions which were obtained, until this fundamental question concerning the presence or absence of reagins is settled.

In this connection the recent report of Chobot[89] is of interest. Testing 53 allergic children with tobacco, he found only 6 of them totally negative. Choosing four of the most marked positives, his attempts to demonstrate the presence of atopic reagins to tobacco in the serums of these patients failed in every case, thus indicating a high incidence of nonspecific cutaneous reactions to this substance in children.

There are certain other considerations which prompt a conservative evaluation of the statistics which have been presented by Harkavy and Sulzberger. First and foremost, there is the element of doubt which arises as to the validity of a comparative study of skin tests in which one of the analyzed groups consists of patients with a vascular disturbance. For, as Lewis and others have shown, the state of the circulation is a vital

factor in wheal formation. Hence, any variations from the normal which may be detected in skin tests on thromboangiitis obliterans cases may rest on circulatory factors and not on immunologic ones.

There is, furthermore, some ground for doubting the specificity of many of the reactions which were reported as positive in the above studies. Referring to his tobacco solutions, Harkavy[79] stated that his "original solutions were irritating and produced false positives." He therefore diluted his extracts ten times for testing. This undoubtedly reduced the number of false positives, but did not eliminate them. That, at least, has been my own experience with the same dilution of the New York Hospital tobacco extract, employed by Harkavy, and designated by him as "Coca's extract." Under the cirumstances, for reasons which have already been discussed in a previous section, it would be decidedly unwise to attach the same significance to doubtful and borderline reactions as to the stronger reactions obtained with tobacco tests. Yet the plus-minus and one-plus reactions comprise a large part of the positive reactions reported by Harkavy[31] in his series. Among his 69 thromboangiitis obliterans cases, 35 out of the 78 per cent who showed positive reactions came under this category, and among the 200 controls 19 out of 38 per cent fell into the same class.

Sulzberger[85] in his studies used some of his extracts undiluted. He, however, was reluctant to include plus-minus reactions in his statistics and counted as significant only those which were at least one-plus or more. Among his 22 cases, 17 gave positive reactions to tobacco, and of these, 7 were one-plus. It is indeed precarious to theorize upon a type of skin reaction in which so great a proportion of the reactions are so slight that they may be confused with reactions which might result from nonspecific cutaneous irritation.

Harkavy, Sulzberger and Trasoff all agree that the incidence of positive personal and family histories of atopy is no higher among thromboangiitis obliterans patients than among normals. This would seem to exclude this disease from the realm of atopic illnesses. Under the circumstances, Harkavy and Sulzberger do not strengthen their position by attempting to demonstrate among their thromboangiitis obliterans cases a high incidence of sensitivity to other atopens. The multiple positive reactions which they report to other substances, such as pollens, animal danders, feathers, foods, dusts, etc., if they can be proved to be specific, would suggest that cases of thromboangiitis obliterans have a *predisposition* to develop sensitivity, which is distinctly characteristic of atopic hypersensitiveness. In the light of the negative atopic background in these cases, one would be at a loss to explain this inconsistency.

Of singular significance is the fact brought out both by Harkavy[31] and by Sulzberger[86] that positive reactions occur as frequently among normal female smokers as among males. Sulzberger admits that no adequate explanation exists as to why this form of hypersensitiveness, which occurs

equally in both sexes, should be the cause of an illness which is found exclusively in males. Nor can one suitably account for the relative infrequency of the illness in a population, which, if one accepts the above reports, is comprised of 30 per cent to 40 per cent of tobacco-sensitive individuals.

The interesting findings of Friedlander, Silbert, and Laskey[90] are pertinent to this discussion. By daily intraperitoneal injections of denicotinized tobacco, these workers were able, within five to twelve weeks, to produce gangrene of the toes in male rats but never in females. There was no suggestion by the authors that these lesions were of an immunologic nature. The sex factor would virtually exclude the possibility that an immunologic process was involved.

Apropos of tobacco hypersensitiveness in relation to peptic ulcers, Ehrenfeld and Sturtevant[91] tested 55 ulcer cases, all but 3 of whom were males and almost all of whom were smokers. Using tobacco extracts in a 1:10 dilution, they found only 2 subjects who gave marked positive skin reactions with pseudopod formation. The Prausnitz-Küstner reactions, even with these two serums, were negative, thus adding to the evidence that many of the positive reactions to tobacco are not specific.

The reported fact that tobacco and histamine react differently upon the human skin[92] or upon the guinea pig uterus[89] does not compel, as an alternative, the conclusion that the action of the former is a specific one. All nonspecific wheal formations are not necessarily pure histamine reactions. (See previous discussion on Wheal Formation.)

Before closing this discussion I wish to state that I have not intended, by the above remarks, to convey erroneously the impression that all tobacco reactions are irritative in nature and not to be trusted. Positive reactions to tobacco often occur, which are as authentic and reliable as those obtained with other atopens. In these, however, as Harkavy and Witebsky[93] and many others have shown, reagins for the tobacco antigen are demonstrable without question by the Prausnitz-Küstner technic.

In view of the fact that so many features of the tobacco hypersensitiveness theory of thromboangiitis obliterans are contrary to immunologic and clinical precedent, one cannot be blamed for manifesting a reluctance to accept this hypothesis until stronger evidence is produced in its favor.

ABSORPTION OF ANTIGEN INTO THE CIRCULATION THROUGH NATURAL CHANNELS

Most of the recent investigations in this subject have tended to corroborate Walzer's[94] earliest contentions that the absorption of unaltered protein from the gastrointestinal tract is a normal and physiologic phenomenon throughout life. The immunologic significance of the finding, however, is still a subject of debate.

Ratner and Gruehl[95] enlarged upon the pioneer experiments of Rosenau and Anderson,[96] who showed that guinea pigs could be sensi-

tized to antigens which were fed to them. Ratner succeeded not only in sensitizing animals to ingested antigens but also in shocking them by the enteral route. As was to be expected, the processes of sensitization and shocking via the enteral canal proved less constant and effective than the customary parenteral methods of administering the antigen in anaphylactic procedures.

Ratner[95] corroborated the direct absorption experiments of Walzer and his associates,[94, 97, 98, 99] using cottonseed and milk as the ingested antigens, thus adding two new proteins to the rapidly growing list of substances previously employed. His subjects included children and adults. He agreed that the entrance of unaltered antigen into the circulation, following its ingestion, is a normal phenomenon at all ages.

Lippard, Schloss and Johnson[100] investigated antigen absorption in infants and children by means of complement fixation tests and concluded that the temporary absorption of food protein, after its initial introduction in ordinary quantities into the diet of the normal infant, "is a physiologic phenomenon." But, whereas in Schloss's[101] earlier studies, in which precipitin tests were employed, the antigen could be detected in the blood for only several weeks, after its inclusion in the diet, the complement-fixing antibodies in the present study were found for a period varying from several months to two years. They interpreted the final disappearance of complement-fixing antibodies to be indicative of a cessation in the absorption of unaltered protein. They therefore doubted that the substances detected by Walzer in the circulation throughout life were truly antigenic and surmised that they were probably haptens.

In the meanwhile, Wilson and Walzer[99] had found the absorption of unaltered egg protein to occur in 72.5 per cent of 62 children varying in age from eleven months to four years and in 100 per cent of four infants less than one week old. In their experiments the lighting up of a cutaneous site, passively sensitized with atopic reagins, which followed the ingestion of the specifically related antigen, was considered an indication of the entrance of this antigen into the circulation. There was no evidence that the immunologic reactions observed in these children differed in any respect from those seen in previous studies on adults on whom the same serum and technic had been employed. There was nothing to indicate that the nature of the absorbed antigen during the first few years of life differed from that during later years.

Up to the present, little has been known concerning the route of entrance of unaltered protein from the intestinal tract into the circulation. Carefully controlled experiments by Alexander, Shirley, and Allen[102] have answered the question. Specimens of lymph were taken from the thoracic duct, the portal vein, and the aorta of dogs who had been fed egg white two to three hours previously. These specimens were tested for egg white antigen by means of precipitin tests, the Prausnitz-Küstner technic, and the Schultz-Dale method using the sensitized guinea pig

uterine strip. The results of these investigations definitely established the fact that the ingested egg white entered the general circulation via the thoracic duct and not by way of the portal vein.

A new approach to quantitative studies on protein absorption was offered by A. Walzer and M. Walzer[11] who presented a method of measuring the "antigen" tide in the circulation. This method consisted of a series of skin tests with a serum of extremely high reagin titer for the antigen which was ingested. These tests were done in succession at regular intervals of one-half hour or more after the antigen meal. They resulted in wheals which increased in their respective sizes for the first hour or two, and then diminished for the next few hours, but did not become negative until the end of the second day. The authors designated this procedure as the "reverse" technic because the reagins were introduced into the skin *after* the antigen meal, in contrast to the usual "direct" technic in which sensitization was performed *before* the ingestion of the antigen.

More intensive investigations of the factors which influence the rapidity of absorption of unaltered protein have been completed. The effect of the degree of gastric acidity has been definitely established by Gray and Walzer.[104, 105] They showed that, in patients with hyperacidity, the absorption of unaltered protein was definitely retarded, whereas in those with hypoacidity or anacidity it was accelerated. They proved, furthermore, that the emptying time of the stomach was secondary in importance to the degree of gastric acidity in influencing the rapidity of absorption. This they accomplished by administering the protein meal directly into the duodenum by means of a duodenal tube. While absorption of the antigen, following its duodenal administration, started, on the average, a few minutes earlier than after its oral ingestion, the same relative effects of the degree of gastric acidity could still be demonstrated with the former as with the latter. The above findings were corroborated by studies with the "reverse technic"[10] which revealed that the administration of dilute hydrochloric acid before the antigen meal definitely diminished the "antigen tide" in the circulation. The oral administration of kaolin, liquid petrolatum, or peptone, before an antigen meal also reduced the absorption of unaltered protein. On the other hand, spiritus frumenti, given with the antigen, was found to hasten its absorption.

The importance of the respiratory tract as a possible route of absorption of unaltered protein was again brought to the fore by Sulzberger and Vaughan.[103] Using silk as an antigen they reproduced the experiments previously performed by Cohen[106] with ragweed pollen. They demonstrated that a cutaneous site which had been sensitized with silk reagins could be excited by the inhalation of a silk powder. Their primary purpose in this work was to emphasize the possibility that

antigens, which are ordinarily considered important as contactants, might also reach the sensitized cutaneous tissues via the respiratory tract.

Almost coincident with these experiments were those of Simon and Rackemann[37] who showed that the absorption of animal serum, following its repeated application to the nasal mucous membrane in atopic individuals, could induce a hypersensitiveness of the skin and mucous membranes in the same manner as did the intracutaneous injection of the same antigen. As a common antigenic relationship between horse serum and horse dander has been definitely established both in human[107] (reaginic) and animal[108] (anaphylactic) experimentation, sensitization to horse serum by respiratory absorption of horse dander may now be considered an established fact.

There have been several recent references in the literature in which it has been stated that absorption of unaltered protein is diminished in atopic individuals. These conclusions were reached as a result of studies on atopic individuals with the passive sensitization technic. The reviewer believes, however, that the diminished reactions which frequently occur in atopic subjects with both the "direct" and the "reverse" methods of study are not to be interpreted as proof of diminished absorption of unaltered proteins in these subjects. The fact[109] that passive local cutaneous sensitization with atopic reagins is less effectively produced in atopic than in normal individuals is a point which must be taken into consideration in these studies as well as in all others in which the Prausnitz-Küstner technic is employed. The use of atopic individuals as subjects for passive local sensitization should be regarded as a violation of proper technic.

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Selected Abstracts

Asthma

UNDER THE DIRECTION OF SAMUEL M. FEINBERG, M.D., CHICAGO

On Simultaneous Occurrence of Bronchial Asthma With Rheumatic Eosinophile Vascular Inflammation. Bahrmann, E.: Virchows Arch. **296**: 277, 1935.

A case of presumable periarteritis nodosa alternating with bronchial asthma is reported in detail suggesting a common allergic hyperergic state in both conditions. The patient was a single woman of thirty-four years who was admitted to the hospital seventy-four days before death. At the age of twenty years she suffered from pain in the right upper abdomen with simultaneous jaundice. Following an attack of angina in her twenty-eighth year, she suffered from a cough with occasional hemoptysis and attacks of dyspnea, occurring chiefly at night. The attacks were often associated with urticaria, especially after eating pineapple. Skin tests revealed allergy to fruit, eggs, milk, and dust. The patient received frequent treatments, including the pneumatic chamber, without relief. The blood repeatedly showed an eosinophilia of 20 per cent to 30 per cent. At thirty years of age she suffered from pain in both buttocks, so that she could not walk. Night sweats and marked weakness followed.

In December, 1934, when the patient was thirty-three years of age, she suddenly developed violent bloody mucous diarrhea. Immediately the asthma subsided, and a large quantity of mucus was expectorated. The sacral and abdominal pain persisted with night sweats and loss of weight in spite of a good appetite. About 5 to 6 stools were passed daily. In view of the clinical picture of ulcerative colitis, a blood transfusion of 300 c.c. was given on the thirtieth day of treatment. This was followed by a slight rise in temperature. As no improvement followed, Kalk's serum shock therapy was tried. Ten c.c. of horse serum was injected intravenously on the thirty-seventh day, and on the fifty-first day a drop infusion of 200 c.c. of horse serum was given to produce shock. The temperature rose and purpura-like spots appeared which subsided slowly. During the succeeding days the condition improved considerably. Later there occurred severe attacks of asthma, with simultaneous immediate cessation of diarrhea, only 2 to 3 stools daily instead of 4 to 5. In the last days a status asthmaticus developed, and the patient died suddenly of heart failure on the seventy-fourth day.

Autopsy was performed thirty-two hours after death, revealing an obliterating pericarditis, chronic pulmonary emphysema with chronic bronchitis (bronchial asthma) and peribronchitis, chronic pulmonary edema; fresh, bilateral, fibrinous pleurisy and old pleural adhesions; hemorrhagic infarction of the cecum and a portion of the ascending colon; bloody effusion into the abdominal cavity, and bilateral hydrothorax. There was a slight swelling of the spleen with perisplenitis; marked congestion of the liver with slight serous chronic perihepatitis. Microscopic examination revealed widespread periarteritis nodosa. The sacral pain may have been due to involvement of the vascular nerves.

Lamb and Otani have also drawn attention to coincidence of periarteritis nodosa and bronchial asthma.

The tissues in the present case showed an extraordinary number of Charcot-Leyden crystals, due probably to sudden destruction of large numbers of eosinophiles. The predominance of crystal formation in the colon suggests a possible local effect of the serum, but particularly the influence of shock therapy on the extensive periarteritic foci of the colon.

Treatment of Asthma by Insulin Shocks. Wegierko, J.: Presse Med. **44**: 731, 1936.

Wegierko treated 40 asthmatic patients with insulin injections of 40 unit doses before breakfast or six or seven hours after a meal. The treatment was given preferably during the asthmatic attack. As soon as the attack had disappeared, sugar was usually administered. The intervals between injections were four or five days in the mild cases and twelve to twenty-four hours in the very severe cases. The insulin shock checks the attack of asthma, and usually after a number of such shocks the course of the disease is favorably modified. The author does not think this form of treatment should be used in persons having cardiovascular difficulty or pulmonary tuberculosis, or in people over the age of seventy.

Asthma and Tuberculin Sensitivity. Jacquelin, A., and Turiaf, J.: Bull. med. de Paris **49**: 911, 1935.

The authors note that asthma of tuberculous origin is most difficult to relieve by ordinary anti-asthmatic methods. These cases are severe. There may be three to five attacks daily, especially at night. In addition there is often an associated dyspnea of permanent type. These patients usually have bronchitis. Relief is obtained only by considering the tuberculosis origin of the asthma and the hypersensitivity to tuberculin.

It was found by these authors that endocrine therapy is often of aid. Intramucosal autoserotherapy and autohemotherapy have also been found useful. They believe that treatment should be directed to latent foci of tuberculosis which constitute a source of sensitization. Gold salts in small doses are used for this purpose, beginning with 0.01 c.c. and increasing by a like amount each time until 0.05 c.c. is reached. The injections are given twice weekly.

An attempt at direct desensitization with tuberculin is also made. Scarifications 1 cm. in length are made on which the tuberculin is applied. The number of scarifications is increased each time until about twelve are made at one time. These treatments are given every two or three weeks.

Asthma of Ovarian Origin. Alice, C.: Bull. med. de Paris **49**: 847, 1935.

The author thinks that certain cases of bronchial asthma in women are of ovarian origin. Attacks of asthma frequently coincide with the premenstrual period, less frequently during the period or immediately after. Attacks also begin at puberty. Aside from these genuine menstrual asthmas there are cases in which marked aggravation of the asthma occurs during the menstrual period. In other cases asthma develops for the first time at the menopause. There are also women who suffer from asthma only during pregnancy.

For several years the writer has used corpus luteum extract in the treatment of asthma of apparent ovarian origin, giving daily injections for the ten days preceding the period. During the days following the period 3 or 4 injections of the patient's own blood are given. Menopause asthma is treated with pituitary-ovarian extracts or with corpus luteum extracts with striking results. Twenty-three cases are reported in detail.

The "Common Cold" and Asthma. Bernton, H. S.: Med. Ann. Dist. of Columbia **5**: 164, 1936.

Bernton discusses the type of asthma which is initiated by an acute respiratory infection or in which the individual attacks follow such infections. In a group of 71 patients of this type 72 per cent gave a positive family history of allergy, while positive cutaneous reactions were obtained in 62 per cent. In this group 38 per cent were children under ten years of age. The point is made that in spite of hereditary history of allergy and high incidence of cutaneous reactions this group of asthmatic persons owe their seizures to "colds" and not to extrinsic allergic factors.

Allergens in Prevention and Treatment of Hay Fever and Bronchial Asthma. Barksdale, I. S.: Med. Rec. **144**: 26, 1936.

The author believes that the oral method of administering allergens is extremely effective in desensitization. The extracts used are aqueous solutions of the allergens. Since he finds skin tests costly and difficult, he omits that procedure and makes no attempt at a specific diagnosis by such methods. He merely extracts the allergens in the environment of the patient and administers them orally. He believes that most patients are sensitive to dust and can be easily relieved by a few daily doses of aqueous dust extract (5 gm. to 200 c.c. water). The doses are usually from 5 to 20 drops. He claims that patients who are not relieved by this dust ingestion are usually helped by the oral administration of a pollen extract. The pollen administered is that found in the patient's environment (without any relation as to the patient's specific sensitiveness). Pollen for extraction was collected by exposing wet cheesecloth on a clothesline and then soaking the cloth in water. Most of the asthma patients improved, while all hay fever patients were successfully treated. For simplicity the above method is certainly supreme. No laborious procedures in specific diagnosis or therapy are required. If the patient is allergic, presumably all that is needed to relieve him in three or four days is to have him drink the washings from the clothes on the line.

Psychological Factors in Asthma. Gillispie, R. D.: Brit. M. J. **2**: 3938, 1936.

The author attaches great importance to psychologic factors in the cause of asthma. He finds that asthma may be implanted in a psychoneurotic personality as the expression of the cumulation of anxiety. Asthma may also be present as a conditioned response to a stimulus with psychologic associations. It may also be evident as an expression of conflict or as a protest against an unwelcome situation or as a means of escape. The author considers that psychogenic factors may be just as important as physical stimuli in precipitating individual attacks. He says that complications and even death may result from asthma, although the latter is of psychic origin. An analysis of the mental difficulty and appropriate psychotherapy is strongly urged.

Blood Groups and Allergy. A Statistical Review. Dyrenforth, L. Y.: Southern M. J. **29**: 617, 1936.

Prospective blood donors presenting themselves for typing at the laboratories of the Jacksonville Hospital (Florida) were questioned about manifestations of allergy (asthma, hay fever and urticaria). Among 322 such individuals 13 per cent had allergic manifestations. On the basis of slight percentage differences among the different blood groups the author expresses the hope that some possible relationship between the phenomenon of allergy and the four blood groups may be found to exist.

Dermatology

UNDER THE DIRECTION OF MARION B. SULZBERGER, M.D., NEW YORK CITY

Use of Autogenous Fungus Extracts in Treatment of Mycotic Infections. Robinson, G. H., and Grauer, R. C.: Arch. Dermat. & Syph. **32**: 787, 1935.

The authors were able to culture fungi from scales on the hands in 31 cases of vesicular eruptions. A series of patients with mycotic infections was successfully treated with autogenous extracts made from pure cultures of these fungi. A method of preparing autogenous fungus extracts for such treatment is described.

Analysis of 66 cases shows that trichophyton was the offender in only 11 cases; aspergillus was most often isolated (17 cases); and alternaria, ordinarily considered nonpathogenic, was obtained in 3 cases in pure culture. Eleven cases were not classified because of difficulty in indentifying the fungus.

Twenty-three patients were treated with a polyvalent stock extract. Nineteen were cured; 3 were definitely improved; 1 showed no improvement.

The authors stress the importance of adjusting the intradermal injections of the fungus vaccine to the individual's reaction.

Report of a case of pulmonary mycotic infection successfully treated with an autogenous vaccine is given.

Of the 66 patients, 49 were cured; 4 greatly improved; 6 improved; and 7 unimproved. Length of treatment varied between the time necessary for 2 injections and fourteen months.

Patients who had received roentgen treatment without benefit were far more resistant than those who had not been irradiated.

Drug or Protein Allergy as a Cause of Agranulocytosis and Certain Types of Purpura. Hunter, F. T.: New England J. Med. **213**: 663, 1935.

The author advances arguments from the literature in support of the theory that agranulocytosis is produced by an allergic mechanism. A past history of allergy in these patients is not common.

To date the evidence of associated pathologic change in the liver is rather scant. Postmortem examinations of many cases of agranulocytosis due to various drugs revealed hepatic changes.

Experimental production of agranulocytosis with drugs known to produce liver changes has been successful. There is evidence that certain foods protect against these changes, and the question arises as to the presence of a substance protective to the liver itself. There is evidence suggesting that the liver may produce a maturing factor for the formation of leucocytes.

Hunter concludes that agranulocytosis is a syndrome rather than a clinical entity, and that it may be produced by a number of substances. "It, together with some allied blood disorders, must probably be placed in the category of allergic phenomena, and may even be conditioned by functional damage to the liver."

Importance of Allergy and Immunity in Skin Tuberculosis. Volk, R.: Deliber. Congr. Dermat. Internat. **9**: 409, 1935.

Volk finds that fundamental principles such as differences of reactions of tuberculous patients, immunity and allergy and their probable identity, and hypersensitivity cannot as yet be definitely defined and classified. Whether the process following an intracutaneous injection of tubercle bacilli may be termed an immunization reaction, or whether it may be regarded as a result of an allergic condition depends

upon the definition of allergy. Volk points out that an important difference between immunity and allergy is that immunity involves neutralization of poisonous substances, while in allergy nonpoisonous substances, combining with the antibody, become highly toxic.

It seems definitely established that the infected organism possesses defense mechanisms, the relative strength of which is an influential factor in the etiology and type of skin tuberculosis.

Aside from the factors of the total strength of defense and the number of bacilli, the site of the first appearance of tissue change is important. If the number of bacilli is small and the quantity of antibodies large, the cutis will be invaded and the different forms of papulonecrotic tuberculosis produced, while indurative tuberculosis finds its beginning in the subcutis.

Investigations Concerning Effects of Bacteriotoxins on Skin. Robert, P.: Arch. f. Dermat. u. Syph. **173**: 267, 1935.

Robert, after investigating the parasitic nature of eczema and testing the epicutaneous effects of bacterial products on both eczematous and noneczematous adults and children, found that bouillon culture products alone caused positive reactions, and that the extract of *Staphylococcus aureus* most frequently was effective. Streptococcus, *B. pyocyaneus,* oidium and trichophyton caused positive results: *B. diphtheriae* and *Proteus vulgaris* did not. The reaction was clinically and histologically the same in all cases. The number of positive reactions was larger than with ordinary eczema tests (patch tests). Eczematous individuals reacted more strongly than noneczematous; children reacted more frequently than adults, although nurslings under one year almost never reacted.

The author points out that these reactions, although typical, must not be regarded as eczemato-allergic, for the possibility of a toxic effect (similar to that of croton oil) must be considered, the results depending on the antitoxin content of the tissues.

Repeated applications of filtrate did not sensitize non-sensitive individuals nor desensitize sensitive ones.

Specificity of the Frei Test in Lymphopathia Venerea. Bacon, H. E.: Am. J. Digest. Dis. & Nutrition **21**: 570, 1935.

Bacon studied 155 patients, of whom 150 gave a positive Frei test. All controls gave negative responses.

Of those with a negative Frei response, 3 gave a positive Wassermann reaction. Even after completion of an antisyphilitic course, they repeatedly failed to give a positive Frei test. Other investigators have reported that in the presence of a recent or active syphilitic process the Frei test may become temporarily inactive.

Bacon concludes that the Frei test has proved specific; and that, in the presence of clinical evidence, one negative test should not be considered to indicate that the process is not one of lymphopathia venerea.

Intradermal Reaction for Chancroids With Chancroidal Bubo Pus. Cole, H. N., and Levin, E. A.: J. A. M. A. **105**: 2040, 1935.

Using an antigen prepared from a proved chancroidal bubo Cole and Levin performed 433 intracutaneous chancroidal tests. Fifty-two were definitely positive, and 272 negative.

Patients with a positive reaction were divided into four groups: (1) those with active manifestations of the disease; (2) those with previous chancroidal infection; (3) those with histories of previous venereal ulcerations and suppurating buboes; (4) those without active infection or history.

In relation to other venereal diseases, the test was negative in 10 cases of lymphogranuloma inguinale, 22 of primary syphilis, 27 of active secondary syphilis, 37 of latent or central nervous system syphilis, 9 of acute gonorrhea, 2 of granuloma inguinale. The remaining negative tests occurred in 50 patients with pulmonary tuberculosis, 26 pregnant women, and 35 patients with various skin diseases, including mycotic infections.

These results appear to confirm previous observations as to the specificity of an antigen prepared from the pus of chancroidal buboes and used as an intradermal diagnostic test. In the experience of the authors, the test is quite specific and is undoubtedly of value in diagnosing certain suspected chancroidal infections in which organisms cannot be found. Apparently the allergic powers in the human body caused by a chancroidal infection, once developed, persist to a certain extent throughout life. [Streptobacillus vaccine has had extensive diagnostic employment and its specificity has long been established.]

Foreign Protein as Auxiliary Factor in Cutaneous Allergy Toward Mercurial Salts and Other "Nonantigenic" Substances. Haxthausen, H.: Deliber. Congr. Dermat. Internat. **9**: 201, 1935.

The author produced, experimentally, specific hypersensitiveness to certain chemicals. This hypersensitiveness was different in only one respect from that observed naturally: it was of surprisingly short duration.

Human serum was noneffective as activator; while horse, sheep, goat, and pig serums were effective.

Allergy toward serum and the mercury components did not develop along strictly parallel lines. The serum allergy was manifest some days before the inception of the mercury allergy and was of almost constant occurrence, while the mercury allergy occurred in only about 50 per cent of the cases. Previous sensitization of the skin with horse serum did not prevent the later development of sensitization toward mercury by a mercury horse-serum antigen.

Haxthausen offers the hypothesis that the microorganisms of the skin may play a part in the pathogenesis of certain allergic cutaneous eruptions, inasmuch as they represent the foreign protein which, in combination with substances applied to the skin, occasions formation of complex antigens capable of producing antibodies. Some microorganisms exert a better activating effect upon haptens than do others. This may perhaps explain the good soil offered by seborrheic dermatitis, with its mixed flora of microorganisms, for the development of allergic states in the skin.

Immunology

UNDER THE DIRECTION OF MATTHEW WALZER, M.D., BROOKLYN

General and Cerebral Anaphylaxis in the Monkey (Macacus Rhesus). Kopeloff, N., Davidoff, L. M., and Kopeloff, L. M.: J. Immunol. **30**: 477, 1936.

Following single or multiple preparatory intravenous injections of undiluted egg white, in generous amounts, fatal anaphylactic shock was regularly induced in monkeys by an intravenous administration of the antigen. Sensitization by the intramuscular, intracerebral, and gastrointestinal routes could also be effected but with less regularity.

Passive sensitization with rabbit anti-egg-white serum was produced in one monkey, and death resulted from the shocking dose of antigen.

Local cerebral anaphylaxis characterized by contralateral focal symptoms and pathologic brain changes including necrosis were likewise observed in sensitized monkeys upon subsequent injection of the specific antigen.

Precipitins could not be detected in the serums at the time of fatal shock. The authors suggest that the antibodies were probably fixed in the tissues and were not present in the circulating blood in amounts large enough to be detected by the usual precipitin test.

There are no characteristic pathologic findings in fatal anaphylaxis in the monkey. In animals sensitized by the intravenous route, marked dilatation of all the cardiac chambers and distention of the stomach are the most frequently noted changes.

Studies in the Variations in the Antistreptolysin Titer of the Blood Serum From Patients With Hemorrhagic Nephritis. I. Control Observations on Healthy Individuals and Patients Suffering From Diseases Other Than Streptococcal Infections. Longcope, W. T.: J. Clin. Investigation **15**: 269, 1936.

The author presents the results of titrations of antistreptolysin in the serums from patients suffering from various chronic diseases and acute infections not caused by hemolytic streptococci.

In the normal series, a titer of between 25 and 50 units was found in 74.5 per cent of cases. In only one individual was the titer more than 100 units. This figure was therefore considered the upper limit of antistreptolysin in the serum from a normal adult. Over a period of observation varying from seven months to a year, the titers in 5 normals and 1 case of hypertension with chronic nephritis remained constant, in spite of colds and attacks of bronchitis.

Among 84 patients suffering with such diseases as diabetus mellitus and exophthalmic goiter, the titer was above 100 units in only 16.6 per cent and in none of these was it above 166.7 units.

In the serums of 66 patients, suffering with such infectious diseases as typhoid fever, bacterial endocarditis, meningococcal arthritis, tuberculosis, and lobar pneumonia, titrations above 100 units were found in 22.7 per cent.

The author could not determine whether these abnormal rises were related to the infecting organism or to an infection by hemolytic streptococci contracted previous to, or in connection with, the acute infection under consideration. Protocols are included.

Studies of the Variations in the Antistreptolysin Titer of the Blood Serum From Patients With Hemorrhagic Nephritis. II. Observations on Patients Suffering From Streptococcal Infections, Rheumatic Fever and Acute and Chronic Hemorrhagic Nephritis. Longcope, W. T.: J. Clin. Investigation **15**: 277, 1936.

The titers of serums from cases of acute infections due to hemolytic streptococci were as follows: Of 19 cases of erysipelas, 68.4 per cent had over 100 units and 31.5 per cent over 200 units; of 18 cases of scarlatina, 44.4 per cent had over 100 units and 11.1 per cent over 200 units; and of 14 cases of tonsillitis, 35.7 per cent had over 100 units and 21.4 per cent over 200 units.

From 55 cases of rheumatoid arthritis, 45.5 per cent of the serums had titers over 100 units and 18.2 per cent over 200 units; while, from 60 cases of acute rheumatic fever and allied conditions, 85 per cent of the serums showed titers over 100 units and 51.6 per cent over 200 units.

In contrast to these findings were those in 18 cases of chronic inactive rheumatic heart disease, in which a titer over 100 units occurred in only 22.7 per cent of cases, none being found over 200 units.

High titers were regularly obtained in the form of hemorrhagic nephritis described by the author as Type A. In another form described as Type B, with insidious onset, the titers obtained rarely exceeded the normal limit. The titer

and the course of the disease could be correlated to a limited degree in acute rheumatic fever and acute hemorrhagic nephritis. The presence of high titers in these conditions is not considered proof that streptococci cause these illnesses, but indicates a recent infection with this organism. Individuals vary in their ability to produce antistreptolysin, and those suffering from acute rheumatic fever and acute hemorrhagic nephritis are particularly prone to form large amounts of this antibody. Detailed protocols are included.

Otolaryngology

UNDER THE DIRECTION OF FRENCH K. HANSEL, M.D., ST. LOUIS

Chondrofibroma of the Trachea. Report of a Case. Gatewood, E. T.: Arch. Otolaryng. **24**: 92, 1936.

An interesting report of a case of chondrofibroma of the trachea by Gatewood emphasizes the importance of bronchoscopic diagnosis in certain cases of dyspnea. The patient had been observed for two or three days with a mild hoarseness and dyspnea, which were regarded as asthmatic. Morphine and epinephrine were administered without relief. Bronchoscopic examination showed an obstruction which had the appearance of normal mucous membrane. Lower tracheotomy was performed with relief of dyspnea. An x-ray examination showed a mass apparently attached to the first and second rings of the trachea. This mass was removed by surgical interference. The patient was entirely relieved of symptoms.

The Value of Bronchoscopy as an Aid in the Diagnosis and Treatment of Bronchial Carcinoma. Ballon, D. H., and Ballon, H. C., J. Laryng. & Otol. **51**: 499, 1936.

The authors emphasized that a cough of insidious onset, purulent expectoration, hemoptysis or asthmatic attacks occurring in an individual of cancer age, must always arouse the suspicion that a malignant tumor of the lung is the underlying cause. It was also pointed out that bronchoscopic examination will permit a positive diagnosis relatively early in over 75 per cent of the cases.

The Fifth, Ninth and Tenth Nerves in Bronchial Asthma. Phillips, K.: Ann. Otol., Rhin. & Laryng. **45**: 373, 1936.

A series of clinical and animal experiments were conducted by Phillips in an attempt to show the relationship of the fifth, ninth, and tenth nerves to bronchial asthma. He states that two mechanisms are involved in the production of bronchospasm—a generalized metabolic abnormality constantly present, and a superimposed trigger mechanism which fires the attack. Evidence was produced to indicate that the trigger mechanism works through the neuro-anatomic reflex pathways. Experimental bronchospasm was produced in both the crucial and living experimental dogs and in the human being by utilizing these pathways. Phillips emphasizes the importance of cooperation between the laryngologist and the internist in all cases in order to combat the problem properly.

The Mechanism of the Bronchial Movements and the Nasopulmonary Reflex. Ellis, M.: J. Laryng. & Otol. **51**: 399, 1936.

The mechanism of the bronchial movements and nasopulmonary reflex was studied by animal experimentation. The structure and dynamic function of the bronchial tubes were discussed and records shown of movements of alterations in

caliber obtained from the interior of a large bronchus of a dog. It was demonstrated that these movements are synchronous with the respiratory movements and are distinct from other rhythmic movements which sometimes occur and which the author does not believe are true peristaltic waves. It was found that powerful stimuli applied to the nasal mucous membrane can evoke reflex, respiratory and bronchial changes, the nature of which, however, is still obscure.

Moccasin Snake (Ancistrodon Piscivorus) Venom Therapy for Recurrent Epistaxis. Goldman, J. L.: Arch. Otolaryng. **24**: 59, 1936.

The clinical studies of Goldman illustrate the beneficial effect of moccasin snake venom in the treatment of recurrent epistaxis. Forty-two patients with recurrent epistaxis without any form of blood dyscrasia were treated with subcutaneous injections of moccasin snake venom. The patients were grouped according to the source of bleeding as follows: (1) telengiectasia of the nasal septum, (2) ulceration of the nasal septum, (3) bleeding without a visible source, and (4) hemangioma of the nasal septum. No other adjuvant treatment was given. The venom therapy was effective in practically all instances either in completely arresting and controlling the nasal bleeding or in markedly diminishing its amount and frequency.

Pediatrics

UNDER THE DIRECTION OF FRANCIS S. SMYTH, M.D., SAN FRANCISCO

Infantile Eczema. Van Rhee, G.: J. Michigan State M. S. **34**: 604, 1935.

The author gives a practical discussion of allergy tests and the factors of irritation from soap, wool, feathers, etc. The various ointments and oil packs he uses are valuable. He finds x-ray useful but light therapy disappointing.

Gastrointestinal Allergy. Ott, M. D.: Iowa State M. J. **26**: 192, 1936.

Colic and migraine in childhood are frequent manifestations of allergy during this period. The author also agrees with Balyeat in the belief that cyclic vomiting is likely to be on allergic basis.

Immune Reactions Induced in Infants by Intestinal Absorption of Incompletely Digested Cow's Milk Protein. Lippard, V. W., Schloss, O. M., and Johnson, P. A.: Am. J. Dis. Child. **51**: 562, 1936.

This report confirms the previous investigations and hypothesis advanced by Schloss and his coworkers, that following initial ingestion of a protein food an appreciable amount of incompletely digested protein is absorbed. From their precipitin and complement fixation tests, they showed the presence of an appreciable amount of the "antigen" for several months even after the antibodies have developed.

The report has considerable theoretical value. The data do not solve the mechanism of protection. They suggest (1) development of impermeability of the intestinal wall; (2) alteration in digestive enzymes so that denaturization takes place; and (3) neutralization by some unknown immune reaction. To the reviewer the last two suggestions are the more likely. They were unable to show antibody or antigen to cow's milk in breast-fed infants, which while not refuting the work of Donnally and his coworkers, does not support the contention of the passage of antigens through the breast milk.

Nasal and Bronchial Allergy in Childhood. Rowe, A. H.: Arch. Otolaryng. **21**: 653, 1935.

Asthma, allergic bronchitis, and hay fever are among the conditions discussed. Characteristically, the author emphasizes dietotherapy and the strict avoidance of likely offending foods. However, he discusses also the rôle of pollens, animal emanations, dust, etc. He states that Urbach's propeptan therapy lacks confirmation, apparently having overlooked the reports from the Vanderbilt Clinic.

Study of Cholesterol Fractions in Acute Infections of Infants With and Without Eczema. Stoesser, A. V.: Proc. Soc. Exper. Biol. & Med. **34**: 10, 1936.

The author finds the cholesterol lower in the presence of infection. This is less marked in older children or in the presence of eczema. The series is small.

Iodine Number of Serum Fatty Acids in Acute Infections of Infants With and Without Eczema. Stoesser, A. V.: Proc. Soc. Exper. Biol. & Med. **34**: 12, 1936.

The iodine values are found reduced in eczema and further reduced by infection. Improvement coincided with a sudden flood of unsaturated fatty acids.

Allergy in Relation to Intelligence and School Success. Sullivan, E. B., and MacQueen, G.: J. Juvenile Research **19**: 173, 1935.

The authors' observations were made in the allergic clinic of Piness and Miller. These psychologists failed to find a preponderance of high intelligence quotients. Performance tests may be irregular since the allergy may interrupt and delay school advance and the usual childhood activities.

The Development of Foreign Protein Sensitization in Human Beings. Mote, J. R., and Jones, T. D.: J. Immunol. **30**: 149, 1936.

This is a valuable report on the development of skin test reaction. They found first a slow (twenty-four-hour) or delayed response, which in time developed to the degree of the usual skin test, characterized by immediate wheal and flare. They found variations in maintenance, loss and development. During the loss of response the process was reversed. Serum antibodies paralleled sensitivity. Intracutaneous injections may sensitize human beings.

Eczema Vaccination. Bradley, D. J.: J. Med. **17**: 14, 1936.

An infant, one year of age, developed superimposed vaccinia from exposure to an older sibling recently vaccinated. This report illustrates the danger with regard to infection, especially cowpox, in infantile eczema.

Some Recollections on Asthma With a Few Suggestions as to Its Treatment in Childhood. Allan, W. D.: Glasgow M. J. **6**: 225, 1935.

The author advises correction of nasal defects and septic foci, regulation of evacuation, avoidance of any "special article of food which upsets the patient," and course of "bronchial asthma vaccine," the use of follicular hormone for girls and of orchitic substance for boys. He apologizes for his unscientific reasoning.

An Enquiry Into the Value of Autohemotherapy in Juvenile Asthma. Maddox, K., and Back, R. F.: Arch. Dis. Child. **10:** 381, 1935.

These Australian workers report an investigation with 24 juvenile patients to whom 10 c.c. injections of their own blood were given. These authors feel that some alleviation of severe symptoms was obtained while at least 75 per cent showed lessened frequency of attacks. Patients with skin sensitivity seemed to respond better than those without positive scratch tests, and the results were also better in patients under ten years of age.

Some Less Common Lung Complications in Asthmatic Conditions in Children. Söderling, B.: Acta Paediat. **17:** 528, 1935.

From his observations at the Caroline Institute, Stockholm, this author calls attention to the difficulty in differential diagnosis when atelectasis complicates asthma. The same holds true for pleural changes which, in the presence of a positive tuberculin test, are liable to be treated as primarily tuberculosis while actually the condition is related to the asthma.

Alimentary Allergy in an Infant. Suner, E., and Larregla, S.: Rev. franç. de pédiat. **11:** 492, 1935.

These Spanish authors (Madrid) discuss the rôle of the intestinal tract in an asthmatic infant. Beans and chocolate were found to be offending foods.

Studies on the Origin of Infantile Allergy. Worringer, P.: Rev. franç. de pédiat. **11:** 283, 1935.

Worringer discusses various theories of origin of infantile allergy. Regarding hereditary factors as opposed to intrauterine or placental transmission, he finds, from careful study of his family background, both male and female germ cells involved. Hence, he cannot accept Ratner's placental transmission theory as the usual mode of sensitization.

Dietetic Treatment of Neurodermatitis in Childhood. Schiff, E.: Arch. Pediat. **52:** 44, 1935.

The author advocates a more empirical program than that usually followed by allergists. A raw fruit and vegetable diet is recommended.

A Contribution to the Knowledge of the So-Called Idiosyncrasies in Infancy and Childhood. Seitz, L.: Monatschr. f. Kinderh. **63:** 310, 1935.

The author reports a case of cow's milk sensitivity in a month-old infant. He had not seen any report on the leucopenic index, but described it in this case, together with a shift to the left in the Schilling differential during the leucocytosis which may follow the fall in white cell count.

Miscellaneous

The Therapeutic Value of Calcium Salts in Serum Sickness. Curphey, T. J., and Solomon, S.: New England J. Med. **214:** 150, 1936.

Of 30 cases of serum disease, 15 alternate ones were treated with large doses of calcium gluconate by intravenous and intramuscular injections. Using a purely objective sign—fading of the rash—as the criterion for therapeutic effect,

it was found that whereas in the control cases the rash persisted for an average of 5.4 days, in the calcium-treated group it lasted but 2.9 days.

When subjective evidence was used as a criterion, the therapeutic effect of calcium was still more striking, for in the control cases symptoms of itching, arthralgia, headache, cramps, nausea, etc., lasted 7.1 days, whereas with calcium the duration was but 3.3 days. Unfavorable reports in the use of calcium salts for serum disease are in all probability the result of insufficient administration of readily assimilable preparations.

Allergic Reactions in the Nervous System. Kennedy, F.: Tr. Am. Neurol. A. **61**: 49, 1935.

The author cites various neurologic disturbances which he believes may be attributed to allergy. These include angioneurotic edema with cerebral symptoms, migraine, certain convulsive states, some cases of retrobulbar neuritis, and allergic encephalitis. Mention is also made of cases of paralysis of the circumflex and long thoracic nerves following administration of tetanus antitoxin; a case of meningeal edema with rapid recovery following the use of scarlatinal prophylactic serum; a patient subject to eczema who suffered successive attacks of blindness, first in one eye and then in the other, due to retrobulbar neuritis. He had a sharp cerebellar seizure, and also a right hemiplegia with abnormal plantar reflexes and severe thalamic sensations over the right side of the body. Another subject with urticaria suffered migrating edemas affecting spinal cord roots with corresponding migrating paralysis.

Attention is called to the important rôle allergy may play in neurologic disorders, and the underlying chemical mechanism is to be sought.

Hypersensitivity to Aminopyrine With Agranulocytosis. Hansen, A. B., and Holten, C.: Ugesk. f. laeger. **98**: 193, 1936.

The authors report a case of hypersensitiveness to aminopyrine with agranulocytosis after about 380 gm. of the drug had been ingested over a period of fourteen months when blood changes were first noted. They attempted to determine whether the reaction in such cases is due to an endocrine disorder. They gave small doses of aminopyrine to patients with various endocrine disturbances but could detect no undue sensitiveness in such instances.

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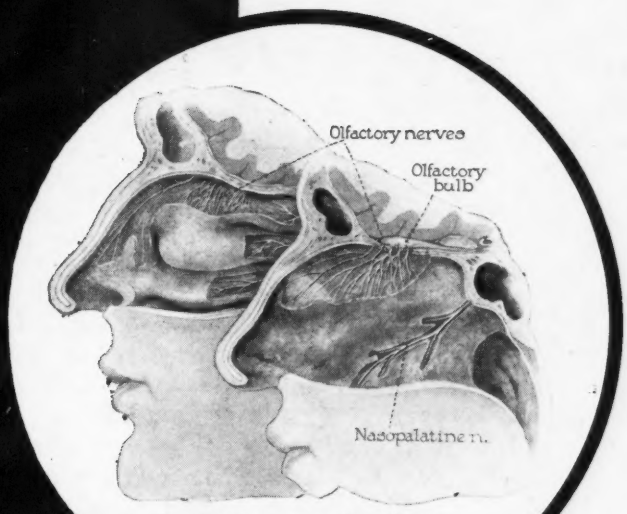

Innervation of nasal turbinates and septum

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(levo-meta-methylaminoethanolphenol hydrochloride)

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Neo-Synephrin possesses definite advantages as a vaso-constrictive agent. It is less toxic in therapeutic doses than epinephrine or ephedrine, untoward systemic symptoms are diminished, and it is without sting at the point of application.

Neo-Synephrin is supplied in the forms of Solution, Emulsion and Jelly, so that the physician can select the product best suited to the needs of the case under treatment.

ACCEPTED AMERICAN MEDICAL ASSN Council on Pharmacy and Chemistry

DOSAGE FORMS

SOLUTION
1/4% and 1%
(1-oz. bottles)

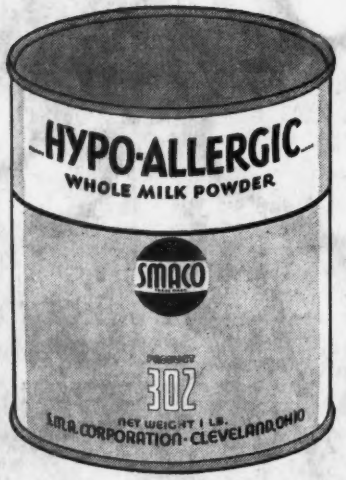
EMULSION
1/4%
(1-oz. bottles)

JELLY
1/2%
(In collapsible tubes with nasal applicator)

FREDERICK STEARNS & COMPANY

DETROIT NEW YORK KANSAS CITY SAN FRANCISCO
WINDSOR, ONTARIO SYDNEY, AUSTRALIA

for Milk ALLERGY



Smaco HYPO-ALLERGIC MILK

CHARACTERISTICS of Powdered Hypo-Allergic Whole Milk (Smaco 302)

Helps prevent eczema in patients hypersensitive to milk protein.

Use present formulas since this is real cows' milk, not a substitute.

Convenience. Individual feedings may be made up for infants.

Lower cost. Powder form costs 25% less than liquid.

Spray dried in equipment reserved for Hypo-Allergic Milk and Alerdex.

It keeps. Hermetically sealed in an atmosphere of inert gas (nitrogen) to prevent deterioration.

We also offer Smaco liquid milks—Smaco (300) Hypo-Allergic WHOLE Milk and Smaco (303) Hypo-Allergic SKIM Milk.

ALERDEX, the PROTEIN-FREE maltose and dextrins

CHARACTERISTICS OF ALERDEX

Helps prevent eczemas when used routinely, due to absence of offending protein.

Use present formulas because Alerdex has same caloric value and percentage of maltose and dextrins.

Does not cake on exposure to air because it is non-hygroscopic.

Dissolves readily in warm water or milk.

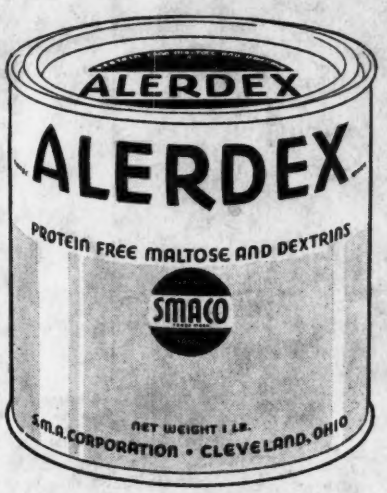
Snow white, free-flowing powder.

Inexpensive—in spite of extra processing under technical control, costs no more.

APPROXIMATE ANALYSIS OF ALERDEX

Moisture	3.0
Ash	0.5
Fat (ether extract)	0.0
Hydrolyzed protein (N x 6.25)	0.5
Reducing sugars as maltose	50.0
Dextrins (by difference)	46.0
Level tablespoons, per ounce	4
Calories, per level tablespoon	27½
Calories, per ounce	110

Alerdex is essentially a mixture of approximately equal parts of maltose and dextrins. It is prepared by a new thermally-controlled process of the enzymic hydrolysis of non-cereal starch, as a result of which it contains no protein contaminant.



S. M. A. CORPORATION - - CLEVELAND, OHIO